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STATUS OF LIVING DIABETICS WITH ONSET UNDER FORTY YEARS OF AGE

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Diabetics are living longer than ever before. So many of them after years of the disease present distressing complications [1] that this article has been written to show that the condition of some of our patients in the younger group after a quarter century of the disease warrants optimism.

These 760 patients with diabetes of 25 years' or more duration fall into four groups: (1) Quarter-Century Victory-Medal diabetics, numbering 23; (2) those with onset in childhood who have survived more than 30 yr., numbering 40; (3) those with onset in childhood who have had the disease between 25 and 30 yr., numbering 181; (4) those whose onset was between the ages of 15 and 40 and who have survived 25 yr. or more, numbering 516.

QUARTER-CENTURY VICTORY-MEDAL DIABETICS

To date [2] no account has been given of the 23 Quarter-Century Victory-Medal patients. Undoubtedly there are many others unrecorded, and I suspect the number will multiply rapidly. Thus, a few weeks ago in the Acta Medica Scandinavica in the Odin Festschrift, Martensson [3] mentioned 10 patients free from trouble with the eyes after 25 yr. of diabetes, but so far as I am aware no other similar statement has appeared in the literature. To find one is a great encouragement. The Quarter-Century Victory Medal is awarded by the Advisory Committee of the Diabetic Fund of the Boston Safe Deposit and Trust Company to those who fulfil the following criteria. These criteria are simple: (1) proof of diabetes of 25 years' duration; (2) a sound body as shown by routine physical examination, with the urine free from albumin; (3) eyes without diabetic complications, such as hemorrhages, exudates, and cataracts, and (4) arteries free from calcification as disclosed by x-rays of the chest, abdominal aorta (lateral view), pelvic arteries, and those of the lower legs between the ankle and knee.

Detection of these cases is not so formidable an undertaking as many think. It is an easy matter to verify the duration of the diabetes; a simple physical examination of the body (including determination of the blood pressure) with a test for albumin in the urine will narrow the number of candidates. This leaves the examination of the eyes to be done, and only if they are perfect will x-ray studies be needful. The cases are so rare that specialists often are happy to do these latter examinations without charge.

The first announcement to give Quarter-Century Victory Medals to diabetics was made in 1947. It was felt that the histories and original treatment of these patients would disclose the cause for their unusually good condition and a hint for methods of treatment to be employed with new patients.

Survival Not Accidental.—Chance coincidence by no means accounts for the survival of these healthy quarter-century diabetic veterans. The more closely their histories are studied, the more definitely do we get indications why they have lived long and remained in excellent physical condition thus far. These 23 patients — and I think it important to add that only nine were our own—lived in unusually favorable homes and under comfortable social circumstances, although I know definitely of but one with sufficient funds to have had the advantage of a private nurse for years. Not one of the patients belonged to the underprivileged class. Three were from physician's families or had relatives who were physicians, and three later became physicians themselves. The physicians who treated them were unusual men, most—but not all—of whom were nationally known as pre-eminent in diabetes. Furthermore, as a rule, there had been continuity of care —no medical shopping, no wandering from clinic to clinic.

Sex: In general occurrence of diabetes is about equally frequent in males and females until the age of 25, but in the Quarter-Century Victory-Medal group females predominated (14 out of 23). I doubt if this is accidental. I think the reason there are more females than males in this Quarter-Century Victory-Medal list is the more faithful attention paid to treatment by girls and young women than by boys and young men. You can

Aided by a grant from the Life Insurance Medical Research Fund.
Aided in statistical analysis by the Statistical Department, Metropolitan Life Insurance Company.
1. Joslin, E. P., and Wilson, J. L.: Lessons for Future Treatment from 472 Fatalities in Diabetic Children, Brit. M. J. 2: 1293 (Dec. 9) 1950.
2. This paper was read before the Los Angeles Society of Internal Medicine, Nov. 1, 1950.
3. Martensson, J., and Palm, E.: Ocular Findings in Long-Standing Diabetes Mellitus, Acta med. scandinav., Supp. 246, pp. 154-165 (June 13) 1950.

say to a girl, "Do you want a baby? Have you heard that until 1883 Bouchardat had never seen a pregnant diabetic woman, that until 1937 Dr. Priscilla White found that only 56% of our pregnant diabetic women had living children, but that since that date 93% have had living children?" Consequently, when my colleagues and I have a diabetic girl we expose her to the pregnant patients awaiting confinement in the hospital and let her see for herself how cheerful and how immune they are to injections of insulin and hormones and to ingestion orally of iron and vitamins and dozens of ammonium chloride pills for the control of edema, all because of the hope set before them that by so doing they will have healthy living children. The diabetes of these pregnant patients is kept well controlled, and the inference is so plain to the diabetic girl that if a pregnant patient can control her diabetes, it surely is possible for a patient who is not pregnant to do so. As for the boys, there is no such appeal. We do ask "Do you want a job? Do you expect to ask us for a recommendation? Do you think a diabetic who fails to control his diabetes should marry your sister?" Be that as it may, a job to a boy is nothing compared with the lure of a baby to a girl.

Heredity: In several of Naunyn's originally reported favorable cases, there was a familial history of diabetes. For several years when seeing a new patient I was cheered to learn there was a relative with diabetes. Later it turned out that the incidence of inherited diabetes was proportional to the period of observation, the group composed of children at onset showing 20% incidence while the group composed of those with diabetes of 20 years' duration showed an incidence of 40%. In the 23 Victory-Medal cases, inherited diabetes is present in 13 out of 21 (two unknown), or 62%, which is about as high an incidence as in any group of ours, except among the identical twin group. Personally, I think this high incidence of inherited diabetes depends on two circumstances—the long periods of observation and the higher social status of the patients. Such a high incidence of hereditary diabetes makes me suspect that a familial history of diabetes would be found for all diabetics if one only knew their ancestry. More and more this high incidence points to the universality of the distribution of Naunyn's diabetic tendency.

Age: The age at onset ranged from 1⅘ yr. to 32 yr., but only one was over 23. The earliest year of onset was 1916; no other case occurred until 1919, another in 1920, and five in 1921. The longest duration of a diabetic thus far has been 34 yr. At present the youngest diabetic is 27 and the oldest 61. Comparable to the latter is a near-medal diabetic, now 63, whom we all considered in perfect condition, but an ophthalmologist found a single small hemorrhage in one eye. Of the 23 Victory-Medal diabetics, 22 live in various parts of the United States and one in Switzerland.

Marriage and Offspring: These diabetics marry. Thus, 17 are married—one later became divorced. The six remaining single consist of one man and five women. Eleven of the 17 marriages have resulted in 28 living children, all of whom are healthy. Obviously, so far as this group is concerned, descendants will be quite limited, and the magnitude of danger from transmission of hereditary diabetes will be small.

Program of Treatment: For 21 of the 23 medal diabetics this was almost identical. The urine was made sugar free by diet or at times even by fasting two days a week; the carbohydrate allowance was restricted for the first three years and often longer to 50 or 75 gm. daily, the protein allowance was moderate, and the fat allowance (after freedom from glycosuria) abundant. The patient's weight was sacrificed to maintain a normal blood sugar and a sugar-free urine. Tests were performed daily, often several times. The diet was weighed and was low in carbohydrate and calories, and the patients today look back upon it realizing how unhappy they were and the relief they experienced when insulin was available, although even then for the next few years the diet remained low.

In the last 15 yr. the diet of all these patients has been liberalized. Although the food is not weighed, all agree they know food values, and, except in a few instances in which there is a boasting spirit of exceeding dietary bounds or negligence, it is absolutely plain that the carbohydrate intake is restricted and is more often less than over 200 gm. daily. All shun excess weight, and even the patient claiming the greatest dietary freedom acknowledges in the same breath that insulin is administered according to the urine tests, frequently made thrice daily.

TABLE 1.—*Age at Onset and Present Age of Twenty-Three Victory-Medal Diabetics*

Age at Onset, Yr.	No. of Diabetics	Present Age, Yr. 25-34	35-44	45-54	55-64
Under 5	2	2	..	..	..
5-9	2	..	2	..	..
10-14	5	..	5	..	..
15-19	10	..	8	2	..
20-24	3	..	..	2	1
30-34	1	..	..	..	1
Total	23	2	15	4	2

Facts regarding the medal diabetics are summarized in Table 2. Unfortunately, some of these data are indefinite because either the patients were so young at onset or their physicians have died. Although only four of these patients ever went into coma, it is clearly evident from the histories that all fell into the severe diabetes group, and, in fact, of the 20 my colleagues and I have classed as having severe diabetes, the average insulin dosage now for 18 is 50 units.

So too about diet. There is no question about its Spartan character at the onset and for two or three years thereafter for at least 17 of the 23 diabetics. The interval between onset and the beginning of insulin therapy was more than two years for six patients. This does not necessarily mean that they had mild diabetes at onset because several of these patients were under the strictest dietetic control; this also applies to two of the three patients in whom the interval between onset and the beginning of insulin therapy was over four years.

All of these 23 patients are taking insulin, but I am in doubt about the number of units taken by three. For the remaining 20, the 24-hr. quantity of insulin ranges from 12 to 100 units. Two patients take between 20 and 30 units, three between 30 and 40, eight between 40 and 50, one between 50 and 60, two between 60 and 80, and four between 80 and 100 in 24 hr. I think the three practicing physicians are those who take the most insulin.

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Medal Diabetics Are Symptomless.—They are free from complications; they have no complaints. They do not even have neuritis. I just hope they will not forget they have diabetes and am thankful they must be pricked each day as a reminder they are vulnerable. There is always more worry over the patient who is allowed to give up insulin than over the one who takes it. The soul of Frederick M. Allen, who in and out of season has preached that diabetes is not progressive, should be cheered. He did so much for me and my patients in the dark preinsulin period that it is a great satisfaction to lay these medal cases at his feet as a tribute to his prophetic insight.

Details of a few of the individual medal cases are given below.

REPORT OF CASES

CASE 1.—It would be relatively easy to explain why a diabetic could be a Quarter-Century Victory-Medal case if all the 23 cases were of similar pattern to the first in the series. This patient's diabetes began in April, 1920, at the age of 14 3/5; it was diagnosed in July of that year when a blood sugar of 333 mg. was revealed. The patient was made sugar free at St. Luke's Hospital, New York, and remained so except for six occasions prior to coming to us in November, 1921, when the urine was sugar free and the blood sugar two hours after ingestion of food 170 mg. His daily diet was 50 gm. of carbohydrate, 90 gm. of protein, and 75 gm. of fat, but later even with insulin therapy the daily diet was only 56 gm. of carbohydrate, 63 gm. of protein, and 150 gm. of fat. At the end of 1924 the carbohydrate allowance was 79 gm., the protein 62 gm., and the fat 140 gm. The blood sugar was 130 mg. after fasting, 120 mg. at noon, and 180 mg. later in the day. From 1925 to 1926 there were no material changes in the diet; the daily dose of insulin was 46 units. In 1927 the daily carbohydrate allowance was 95 gm. In 1930 the daily diet allowance was 115 gm. of carbohydrate, 75 gm. of protein, and 140 gm. of fat. As late as 1937 the daily carbohydrate allowance was only 125 gm., the protein 90 gm., and the fat 120 gm. The patient weighed 158 lb. (71.7 kg.) and took insulin three times a day in doses of 25, 7, and 25 units respectively. In 1940 the daily carbohydrate allowance was 140 gm., and at present the daily diet allowance is approximately 180 gm. of carbohydrate, 100 gm. of protein, and 115 gm. of fat. The patient now weighs 158 lb.

This patient for the first seven years had perhaps our best-trained diabetes nurse, never was known to break diet, and lived actively. On weekends he flew his own airplane alone with his nurse from New Jersey to Cape Cod. He wandered over the world and was perhaps our first patient deliberately to reduce his insulin intake in anticipation of exercise, such as playing tennis in the Bois de Boulogne in Paris. Later this patient was again wonderfully fortunate in marrying a young woman who spent months in learning how to care for him. Since this time he has been most active in a large business; in 1935 he told me he had only missed five-and-a-half days from work in many years. He has three healthy children. This man is 6 ft. 2½ in. (189 cm.) tall and weighs 154+ lb. (69.9 kg.) dressed. He was in such abounding health that he received unanimous applause in 1947 at a meeting of the Association of Life Insurance Medical Directors of the United States and Canada. In 1946 in a railroad accident in which many were injured, he suffered fractures of eight ribs, the scapula, and the radius, but his surgeon at Roosevelt Hospital at the end of a month said his recovery was as rapid as that of a nondiabetic. This man had not only everything that money could buy to protect him but also a wonderful family, friends, and his own character and zeal to make life successful.

TABLE 2.—*Data on Victory-Medal Diabetics*

Year of onset	1916-1925	
Age at onset, yr.	14½-32	
Sex—Females	14	
Males	9	
No. with inherited diabetes	13	
Degree of diabetes—Severe	20	
Mild	3	
No. on rigorous diet at onset, usually including fasting	17	
Interval between onset and beginning of insulin therapy		
Within 1 week	4	23
1-3 mo.	4	
4-6 mo.	3	
1 yr.	3	
2 yr.	3	
4 yr.	2	
5 yr.	1	
6 yr.	2	
Unknown	1	
Present insulin dose, units	12-100 (48 average of 21 patients)	
Marital status—Married	17	
Single	6	
Divorced	1	
No. of offspring	28	
No. actively working at home or in business	22	

CASE 2.—A somewhat similar case is that of a conscientious girl whose age at onset in March, 1922, was 14 1/10 yr. and whose devoted, highly educated, and meticulous parents helped her supervise her diabetes for 27 yr. until her marriage. She was seen more frequently by us than any of our other medal diabetics, and the control of the diabetes is shown by her blood sugar values, which ranged close to reaction levels and only on the rarest occasions rose above 230 mg. in over 20 yr. The original diet was a daily allowance of 95 to 118 gm. of carbohydrate, 70 gm. of protein, and 106 to 150 gm. of fat. Her daily insulin dose is now 37 units.

CASE 3.—In this patient diabetes developed in 1921 when the patient was nine years old. A daily diet of 54 gm. of carbohydrate, 66 gm. of protein, and 42 gm. of fat was prescribed. The patient was maintained on approximately this diet for several years. The insulin dose at present is 36 to 44 units daily.

CASE 4.—Illustrations of the strenuousness of the diet are furnished by this case. Onset of diabetes occurred in January, 1923, when the patient was 1 4/5 yr. Even with the use of insulin in 1926, the patient, while weighing 39 lb. (17.7 kg.), ate only 45 gm. of carbohydrate, 46 gm. of protein, and 90 gm. of fat daily. In 1949 the daily insulin dosage was 30 units of regular insulin plus 10 units of globin in the morning and 20 units of regular insulin plus 20 units of globin in the evening.

CASE 10.—This patient's age at onset in 1924 was 9 4/5 yr. His diet was more than strict; he ate washed bran, lean meat, branwafers, and "tons of vegetables." He grew little and had insulin reactions while on the very low diet. Urine tests were made two to three times daily, and in the early years every bit of food was weighed on a gram scale. His present insulin dose is 88 to 93 units daily. Upon the basis of his being a Victory-Medal diabetic, I successfully pleaded with the government to allow him to retain a Federal position.

CASE 11.—This patient's age at onset in 1921 was 32. She evidently had a mild case of diabetes, and her diet was not as rigid as those heretofore described. She is an example of the many diabetics who by faithful adherence to treatment should easily earn a Victory Medal. Her daily insulin dose is now 20 units.

CASE 12.—This patient's age at onset in 1923 was 15 3/10 yr. She was on a most rigid diet for three years. At the end of three years her daily carbohydrate allowance had been raised to between 60 and 75 gm. The patient cannot remember eating any portion of food which weighed over 3 oz. (90 gm.).

CASE 13.—This patient's age at onset in 1923 was 15 yr. A very strenuous diet was prescribed at the start. He was the first person in New Mexico to use insulin. His insulin dose at present is 72± units daily.

CASE 17.—Diabetes developed in this patient in 1923, when she was 18. A fairly strict diet was prescribed, the daily carbohydrate allowance being 50 gm., the protein 70 gm., and the fat 150 gm. for many years, except when her weight went up and the fat allowance was restricted to 50 gm. daily. The patient took her diabetic life most seriously and was much disturbed if sugar ever appeared in her urine. She made every effort to keep her urine sugar free. Her present insulin dose is 48 units daily.

DIABETICS WITH DIABETES OF THIRTY YEARS' DURATION WITH ONSET IN CHILDHOOD

Corroborative testimony that diabetics are living long and—most of them—useful lives is afforded by 40 of our patients with diabetes of 30 to 35 years' duration whose onset was in childhood. Only one of them, so far as my colleagues and I are aware, is a Victory-Medal patient, but 33 are working steadily. Of the remaining seven, one is temporarily out of work, one is a manic depressive, two are incapacitated, and details about three are wanting. Of this group is a man whose age at onset in July, 1920, was 14⅘ yr. He is at present head of the Parent-Teachers' Association, the Boy Scouts, and President of the Crippled Children Scouts in his locality. Another patient was the only child to have survived coma before the discovery of insulin, and another was the first child to have received insulin at our own hands.

Twenty-three of the 40 patients are men and 17 are women. The incidence of hereditary diabetes is again prominent in this group—62%. Thirty-one of the 40 have married, resulting thus far in 41 children in 21 families, of whom nine are in Dr. Priscilla White's pregnancy series. Of all our women, only two have had as many as four living children, and the number who have borne living children after 25 yr. of diabetes can be counted on the fingers of one hand. My colleagues and I know of only two divorcees in this group, one man and one woman, although the man subsequently remarried.

Calcification of the arteries as shown by x-ray examinations, from a slight trace to a 4 + reading for 22 patients (or 63%), was found in the 35 in whom this complication was sought. The eyes of 30 have been examined by accredited ophthalmologists. Nineteen showed arteriosclerosis of the vessels of the retina; 17 were found to have retinal hemorrhages. In 13 of the latter, exudates were also found, and five have retinitis proliferans. Only one patient, however, can be said to be incapacitated because of the eyes. None is blind. In one patient with retinitis proliferans coronary cataracts also developed. Of the 10 patients whose eyes were not examined, one is reported by his local doctor as "having early retinitis." One has written that he has a "hemorrhage in the right eye," and one is taking rutin "because of trouble with his eyes," which suggests that of the 40 patients some degree of diabetic involvement of the eyes has developed in a probable 33 (or 82%). I would emphasize that 18% may have good eyes, just as my colleagues and I found this to hold for the 23 medal diabetics. Even if there was only one with eyes intact, I would be encouraged. There must always be a beginning in any series.

High blood pressure, ranging from minimal readings of 145/80 to 210/110, was found in 15 (37%) of the entire group, and 10 patients (25%) have shown varying degrees of albuminuria from 50 to 1,000 mg. per 100 cc., but I am happy to add that of the 13 patients tested within the past year, five were still free from any trace of albumin in the urine. Up to this year tuberculosis had developed in none of the 40 patients. This month x-rays of another patient have shown a questionable shadow in one lung, but as yet there has been no definite diagnosis of tuberculosis. Epilepsy was diagnosed in but one instance.

The rigidity of treatment in the early years is illustrated by a girl who weighed 46 lb. (20.9 kg.) in 1923, when she was 14⅘ yr. Despite this undernutrition, by 1947 her weight was 142 lb. (64.4 kg.), and she writes that her son, born years after onset of her diabetes, weighs 135 lb. (61.2 kg.) and is 5 ft. 7½ in. (171 cm.) tall.

DIABETICS WITH DIABETES OF TWENTY-FIVE YEARS' DURATION WITH ONSET IN CHILDHOOD

This group includes 181 patients who already have had diabetes for 25 to 30 yr. Of these, 81 are men and 100 women. One hundred and twenty-six are married, of which 53 are men and 73 women. Two of the women have married twice and one three times. Three we learn have been divorced. Eighty of these 181 patients so far have 111 living children, and several are "expecting." Four have adopted children. Indeed, we have one diabetic mother who, losing her own child, adopted the illegitimate child of another of our diabetics.

Eyes.—Various data about the eyes, presence of albumin in the urine, blood pressure, and condition of the arteries are given below. These data were not synchronously obtained, but they give a hint as to the general picture. Of the 114 examined by ophthalmologists, arteriosclerosis of the retinal vessels was found in 56 (49%) and retinal hemorrhages in 57 (50%); 23 of the latter also showed exudates. Seventeen patients have retinitis proliferans, and in six cataracts have developed. Four patients are almost or entirely blind; three are blind in one eye; one is reported to have extensive detachment of the retina, and one is temporarily unable to work because of retinal hemorrhages.

Albuminuria has been recognized in values ranging from 50 to 1,020 mg. per 100 cc. in 32 (18%) of the 181 patients. However, many have not been examined recently. This is in marked contrast to the figure of 51%, which represents the proportion of deaths from kidney trouble among our 135 deaths among juveniles between 1944 and January, 1950. The blood pressure of 61 (34%) has shown readings of 145/80 or above. Arteriosclerosis has been discovered in 71 (59%) of the 121 patients examined by x-ray.

Psychological difficulties of sufficient severity to require treatment, ranging from anxiety neurosis to acute reactive depression necessitating electric-shock therapy, have developed in 11 of the 181 patients. In addition, two patients have become psychotic, requiring institutional care. One of these even received the Victory Medal. One patient is suspected of having petit mal, and one patient reports having been operated upon for epilepsy. Pulmonary tuberculosis was found in five patients.

Four of the 181 have received the Victory Medal, and several are now being considered as possible future recipients of the honor. Five in the group are successful practicing physicians, and one patient is presently employed as head nurse on the delivery floor of a nationally famous hospital.

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DIABETICS WITH DIABETES OF TWENTY-FIVE YEARS' DURATION WITH ONSET BETWEEN FIFTEEN AND FORTY YEARS

There are 516 of these patients. One hundred and eighty-eight had treatment with us before our first patient received insulin, Aug. 7, 1922, and another 118 fell into our hands before 1926. The remaining 210 patients received treatment elsewhere before my colleagues and I saw them.

Sex.—In this group there are 273 men and 243 women.

Race.—Among all our patients 16.2% are Jewish, and among these 516 quarter-century diabetics the percentage was essentially the same—18%.

Heredity.—The incidence of hereditary diabetes here as in all long-duration diabetes groups was high, namely, 44%; among the men it was 32% and among the women, 53% (as usual higher). So marked a divergence between the sexes in the incidence of hereditary diabetes I do not remember having encountered before.

Marriage.—Only 42 of the 273 men and 31 of the 243 women were single. Seventy-nine per cent, or 410, were married. Eight of the 516 had been divorced.

What is the present status of these 516 diabetics whose onset was between the ages of 15 and 40 with 25 yr. of diabetes behind them? Information was sought for nine items from the records and letters later received from patients and physicians: (1) use of insulin, (2) whether the patient is working or active at home, (3) presence of albumin in the urine, (4) presence of high blood pressure, (5) condition of the eyes, (6) whether amputation of an extremity had been done, (7) manifest presence of arteriosclerosis, (8) presence of cardiac disease, and (9) presence of cerebral involvement. Data were missing in many of these categories. Consequently, it was decided to report upon only those diabetics for whom we had definite knowledge of at least six of these nine topics. Data regarding 63 of the patients seen earliest in the series and 41 seen latest were analyzed.

Present Status.—It is apparent that practically all of the patients are taking insulin—98.4% and 92.7% of the two groups respectively. Approximately 80% are active, although they are far above the age of 40, and their ages now range up to 65 or more. Albuminuria was reported in about 20% but a high blood pressure or involvement of the eyes in about 50%, with fully two-thirds of these showing arteriosclerosis. Heart disease was seen in slightly more than 25%, but only four patients had histories indicating cerebral involvement. Only nine of the 104 whose cases were analyzed had an amputation of an extremity.

SUMMARY

Such is the condition of our 25-yr.-duration diabetics. A few are perfect, and approximately 80% are active. The patients in perfect condition are those whose treatment was initiated (with hardly an exception) with strenuous control of the diabetes in their early years, this control being maintained for 10 yr., more or less, to more than the usual extent and even then continued. As in Dr. Priscilla White's [4] series of children's cases, as in the youthful cases reported by Root, Sinden, and Zanca,[5] and as in the 247 cases recently studied and soon to be published by Root, Wilson, and Marble,[6] so in this series the evidence is overwhelming that strict treatment of diabetes pays and, moreover, that control of the disease is possible. I grant that the life of a diabetic child or young adult even today is no flowery bed of ease. I acknowledge that tuberculosis, coma, and renal disease are far too frequent in young diabetics, but I think one is justified in saying that in a diabetic arteriosclerosis need not be premature.

81 Bay State Rd. 15.

4. White, P., and Waskow, E.: Arteriosclerosis in Childhood Diabetes, Proc. Am. Diabetes A. **8**: 139-151, 1948.

5. Root, H. F.; Sinden, R. H., and Zanca, R.: Factors in the Rate of Development of Vascular Lesions in the Kidneys, Retinae and Peripheral Vessels of the Youthful Diabetic, Am. J. Digest. Dis. **17**: 179-186, 1950.

6. Wilson, J. L.; Root, H. F., and Marble, A.: Prevention of Degenerative Vascular Lesions in Young Patients by Control of Diabetes, Am. J. M. Sc. **221**: 479-489, 1951.

PNEUMOCOCCIC MENINGITIS IN INFANTS AND CHILDREN

COMBINED THERAPY USING PENICILLIN AND SULFONAMIDE

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The steady advance in therapy in the past decade with the introduction of new chemotherapeutic agents and the antibiotics has dramatically influenced the fatality rate of pneumococcic meningitis. It is now a question of not only which agent or combination of agents to use, but also of how each agent can most effectively be applied. In the treatment of meningitis, especially, the known irritation and possible danger of intrathecal medication must be weighed against the seeming necessity for its use in a usually fatal disease.

Penicillin was first used on the Children's Service at Bellevue Hospital in the treatment of pneumococcic meningitis in May, 1943. The following report will concern itself with patients seen only since this time. Fifteen infants and children were treated between May, 1943, and December, 1949.

Pneumococcic meningitis was almost universally fatal before penicillin and sulfonamide therapy. Rarely did a child survive. Of 150 patients from the Harriet Lane Home, Baltimore, as reported by Waring and Smith [1] in 1944, there were no recoveries. The disease was almost

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Tables 2 and 3 have been omitted owing to lack of space. They are included in the reprints.

1. Waring, A. J., Jr., and Smith, M. H. D.: Combined Penicillin and Sulfonamide Therapy in the Treatment of Pneumococcic Meningitis, J. A. M. A. **126**: 418 (Oct. 14) 1944.

invariably fatal at the Children's Hospital, Washington, D. C., where Ross and Burke [2] described one recovery in 66 patients. All of the 157 patients observed by Toomey and Roach [3] succumbed, as did those in our own experience prior to 1943.

The use of sulfonamides changed the fatal outlook slightly, as illustrated in the series of Waring and Smith [1] with one recovery out of 17. The combined use of antipneumococcus serum and sulfonamide further improved the prognosis. Ross and Burke [2] reported 10 recoveries in 38 cases, and Sweet and his associates [4] described three survivals out of a group of 40 patients, one-half of whom received both sulfonamide and type-specific antiserum. Combining the results reported from other institutions with those in Children's Hospital, Ross and Burke found that the fatality rate using both agents was still high, ranging from 58 to 70%. Dowling [5] had four recoveries in 72 cases.

The addition of penicillin to the therapy of pneumococcic meningitis introduced the new era in the prognosis of this disease. Using penicillin alone, Sweet and co-workers [4] reported seven recoveries in 16 patients.

The purpose of this study is to give the excellent results using the combined therapy, sulfonamides and penicillin, in 15 consecutive patients. Fourteen recovered from the acute infection, and only one of these had residua. The 15th patient was moribund on admission and died 27 hr. later.

MATERIAL

All patients with pneumococcic meningitis seen on the Children's Medical Service, Bellevue Hospital, between May, 1943, and December, 1949, are here reported. They were treated with penicillin and sulfadiazine as well. The ages of the patients ranged from 4 weeks to 11 yr., nine being well under 1 yr. of age, and seven were under 6 mo. It is significant that recovery without residua was obtained in two babies under 6 weeks of age treated, and in a third, who was a premature baby, weighing 8 lb. 12 oz. (4 kg.) and being 4 mo. of age at the time of infection. Thirteen of the 15 cases were observed from October through May, coinciding in seasonal incidence with the period cited by Ross and Burke [2] in their more extensive series of 64 cases.

CLINICAL FINDINGS

Twelve of the 15 patients were seen early in the course of the disease, from six hours to two days after onset. One of these was admitted with a febrile illness of only one day and evidence of meningitis developed 48 hr. after admission to the hospital. On the other hand, one infant, who was first seen late in the disease, had a febrile illness of two to three weeks, with clinical signs of meningitis for at least five days previous to admission. Hydrocephalus in this patient developed and he died nine months after the infection with meningitis.

Although most of these patients were seen early, the diagnosis of meningitis usually was made readily on admission. Of the 15 patients, 11 had obvious signs leading to the immediate diagnosis of meningitis. A stiff neck had been found in five of these before admission to the hospital and three others had convulsions. There were four, however, in whom the diagnosis was elusive. Two patients were first admitted to other services, one to surgery and one to otolaryngology, because of swelling below the left ear following a long-lasting respiratory disease. In both instances the diagnosis of pneumococcic meningitis was established 24 hr. later.

The difficulty of diagnosing pneumococcic meningitis in young infants must be emphasized, and the consequent later diagnoses may in part account for the higher fatality rate in this age group. Neurological signs may be absent early in the disease. Cases 3 and 14 were particularly instructive in this respect. Both infants were brought to the hospital because of convulsions and fever and hence were examined carefully for signs of meningitis. In Case 3 neurological signs were not found until eight hours after admission, even though the spinal fluid on admission was turbid and clearly indicated a meningeal infection. In Case 14 the problem was even more difficult. Repeated neurological examinations were negative, and since the spinal fluid was clear and its chemistry was normal, a diagnosis of meningitis could not be made until a positive spinal fluid culture for Pneumococcus Type VI was obtained 20 hr. later. At this time a second spinal tap revealed a purulent fluid with marked cellular reaction. Here, then, was an infant with extensive bacteremia and bacterial invasion of the spinal fluid producing repeated convulsions without associated neurological signs.

One month later a newborn infant, Case 15, was seen with a somewhat similar history of convulsions and fever, but of longer duration. Again, a neurological examination was negative and the fontanel was flat, but the spinal fluid was cloudy and contained some cellular reaction. A smear of this fluid showed numerous gram-positive diplococci. Here, again, there was obviously extensive bacterial invasion of the spinal fluid, probably early, which would not have been diagnosed without the aid of the spinal fluid studies.

Physical examination alone is often deceptive and cannot be relied on for a diagnosis of pneumococcic meningitis in young infants. The commonest finding in infants under a year was a bulging fontanel, which was discovered in six of the nine infants in this series.

Meningitis developed under observation in Case 8, in whom the first study of the cerebrospinal fluid indicated a serous meningitis, i. e., negative culture and a mild lymphocytic cellular reaction. The second cerebrospinal fluid specimen, obtained 24 hr. later, showed an increased cellular reaction of polymorphonuclear cells and a positive culture for Pneumococcus Type XX. In this instance a slightly stiff neck without any other neurological findings was observed on first examination.

The neurological examination alone was adequate to diagnose meningitis in 10 of the 15 patients either be-

2. Ross, S., and Burke, F. G.: Pneumococcal Meningitis in Infants and Children: A Report on the Use of Combined Sulfonamide and Penicillin Therapy, J. Pediat. **29**: 737, 1946.

3. Toomey, J. A., and Roach, F. E.: Pneumococcic Meningitis, Ohio State M. J. **35**: 841, 1939.

4. Sweet, L. K.; Dumoff-Stanley, E.; Dowling, H. F., and Lipper, M. H.: The Treatment of Pneumococcic Meningitis with Penicillin, J. A. M. A. **127**: 263 (Feb. 3) 1945.

5. Dowling, H. F.; Dauer, C. C.; Feldman, H. A., and Hartman, C. R.: Pneumococcal Meningitis: A Study of 72 Cases, New England J. Med. **226**: 1015, 1942.

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cause of a stiff neck, Brudzinski sign, ankle clonus, or spasticity.

In all 15 cases pneumococci were grown from the spinal fluid and typed. Direct smears from the spinal fluid are of real value in guiding the immediate therapy and should be done always. Attention to morphology as well as reactions to gram-staining will help prevent the occasional error in staining technique. In Case 15 in this series a smear of the spinal fluid showed abundant gram-positive organisms far out of proportion to that expected with the low cellular reaction in the spinal fluid.

Eleven patients had positive blood cultures. In one of these the first blood culture taken together with the simultaneous spinal fluid was sterile; however, for the next three successive days pneumococci were grown from the blood stream. In the remaining four patients the blood cultures remained sterile.

Nose and throat cultures were taken on 12 patients, and, from 10 of these, pneumococci were cultured which, when typed, were found to be the same type as that in the spinal fluid.

In all patients an effort was made to locate the focus for the pneumococcic infection. X-rays of the chest were taken on all patients, and, when indicated, mastoid and sinus x-rays as well. There were 10 patients in whom a focus was found either by physical examination or by study of x-rays. In two of these, purulent otitis media alone was found; in another two there was x-ray evidence of infection in the maxillary sinuses and in the mastoids —one of the latter patients also had pneumonia. Only two infants had pneumonia clinically, one diagnosed by x-ray evidence alone, and clinical signs of bronchopneumonia developing in the second shortly after admission. In a third infant, Case 15, early lobular pneumonia, apparently not the focus for the meningitis, was found only at autopsy.

THERAPY

As soon as the diagnosis of meningitis was established, all patients were given penicillin intramuscularly and sulfadiazine orally, the latter usually in dosages of 1½ grains (0.10 gm.) per pound of body weight. Fourteen of the 15 patients received intrathecal penicillin as well, although three of these had only one such treatment given in the beginning of the disease. In two desperately ill patients, specific antipneumococcus serum was also given. In one of these, Case 9, heparin was administered intrathecally on three occasions, as suggested by Ross and Burke [2] for the prevention of adhesions that might obstruct the flow of the cerebrospinal fluid between the ventricles and subarachnoid space. (In the future streptodornase and streptokinase might be employed for this purpose.) Though desperately ill, this patient survived the acute infection, but was left with severe central nervous system damage and died nine months later.

Intrathecal therapy with penicillin was used as soon as the diagnosis was confirmed bacteriologically in 14 of the 15 patients and was continued in 10 of these until the fluid was sterile. There was considerable variation in the amount and duration of intrathecal penicillin therapy. Clinical judgment is important in guiding the therapy, taking into consideration such factors as the age of the patient, duration of illness prior to beginning treatment, and severity of infection. In this series the single dose of intrathecal penicillin has varied from 5 to 20,000 units in all except Case 6. Lately, we have usually given 10,000 units to children and 5,000 or less to infants, per day.

Equally important with the dosage of penicillin is the number of intrathecal injections both as regards meningeal irritation, sensitivity reactions to the antibiotic, and efficacy of therapy. Of the 15 patients in this series, only three were treated intrathecally longer than six days. An average of five intrathecal treatments with penicillin was given to 11 patients; five of these had three or less injections. The patients described by Hutchins and Davies [6] averaged 11 intrathecal treatments with some patients receiving two to three treatments a day, and those of Ross and Burke [2] averaged six treatments. The fatality rate of these two series is higher than that of the present report, being five patients of 14, and three of 19, respectively. Appelbaum, Nelson, and Albin [7] more recently suggested three to five injections. The fatality rate in their series was 18.2% for 44 patients under 11 yr. There are many factors influencing fatality, but it is suggested that more intrathecal treatment did not give a better prognosis.

Particularly significant as regards intrathecal therapy is Case 7, a 4-week-old infant whose spinal fluid could only be removed by negative pressure because of the abundance of thick purulent exudate. Because of mechanical difficulties no more than two small intrathecal injections of penicillin of 2,000 units each could be given, and yet the patient recovered.

RESULTS

Fourteen patients recovered from their pneumococcic infection; in one hydrocephalus developed and he died nine months later. Two of the cured patients were 1 mo. and 6 weeks of age, respectively, at the time of the infection. One infant of 42 days was moribund on admission and died 24 hr. later. There were nine patients under 1 yr. of age.

A follow-up study of all patients surviving was made at intervals ranging from six months to five years after the infection. All patients were well and manifested no residua attributable to the pneumococcic infection. One child, however, had a reading disability, and a second had a severe behavior problem, probably resulting from infantile hydrocephalus which had existed for many years before the pneumococcic meningitis. Electroencephalography was not done in these patients.

COMMENT

The change in the almost universally fatal prognosis of pneumococcic meningitis with the use of combined therapy, penicillin and a sulfonamide, is most impressive. Analysis of the cases from the literature revealed that of 158 children treated with this combined therapy, 128 (81.0%) lived.

6. Hutchins, G., and Davies, J. A. V.: Penicillin Treatment of Pneumococcus Meningitis in Infants, J. Pediat. **27**: 505, 1945.

7. Appelbaum, E.; Nelson, J., and Albin, M. B.: The Treatment of Pneumococcic Meningitis with Penicillin, Am. J. M. Sc. **218**: 260, 1949.

Of the nine patients in this series under 1 yr. of age, all except two were admitted to the hospital within 48 hr. of onset of the disease. These two were the ones who failed to recover promptly, one dying within 27 hr. and hydrocephalus developing in the other who died nine months later.

An analysis of the prognosis in our series with regard to age of the patient and duration of the disease prior to treatment was made. Clearly, patients seen late in the disease have a poorer prognosis; the two patients who failed to respond were seen after the fourth day of disease and both were under 1 yr. of age.

A composite study of pneumococcic meningitis as reported in the literature with reference to prognosis and duration of disease at the time of treatment was made. The fatality rate of patients treated not later than the first 72 hr. (42 cases) is 11.9%. Thereafter the chances of recovery decrease in proportion to the length of time of the disease before treatment is begun. For all cases studied, 105, the fatality rate was 24.8%; whereas for the 33 treated after the fifth day of disease, 42.4% died.

Although in the small series here presented the results were highly satisfactory, the question arises as to whether the same success might be achieved with less strenuous therapy. Is intrathecal therapy necessary? One patient in our series demonstrated the possibility of complete recovery without it.

The danger of intrathecal therapy with any form of foreign material is well known. Three of our patients had convulsions from one to four hours after intrathecal penicillin was given. Only one of these had had convulsions previous to intrathecal therapy, but this child continued to have severe convulsions after each intrathecal treatment. This irritative effect of antibiotics on the central nervous system has been previously noted. Reuling and Cramer [8] report a case of convulsions in an adult patient receiving 500,000 units of penicillin. This patient recovered, however, without sequelae. Johnson and Walker [9] report one case showing convulsions after a massive treatment, receiving 100,000 units intramuscularly in an infant. Other observers [10] also report reactions which are thought to be due to the penicillin itself, either because of impurities or because of excessive dosages of the antibiotic.

TABLE 1.—*Outcome of Pneumococcic Meningitis in Relation to Treatment*

Age	Duration Before Admission	Penicillin: Intrathecal: Number of Treatments	Penicillin: Intrathecal: Total Dose, Units	Penicillin: Intramuscular: Total Dose, Million Units	Penicillin: Intramuscular: Duration in Days	Sulfadiazine by Mouth: Total Dose, Gm.	Sulfadiazine by Mouth: Duration in Days	Outcome
Age Group Under One Year								
1 mo.	6 hr.	2	4,000	10.8	23	6	16	Recovered
1 mo.	12 hr.	1	10,000	12.6	17	40	20	Recovered
1½ mo.	1 day	0	0	0.4	6	38	25	Recovered
5 mo.	1 day	?	?	0.7	6	5	4	Recovered
3 mo.	1 day	6	35,000	25.6	19	13	17	Recovered
4 mo.	2 days	18	330,000	13.9	46	25	42	Recovered
1½ mo.	4-6 days	1	5,000	1.8	1	1.5	1	Died
10 mo.	5 days	10	100,000	11	12	23	16	Brain atrophy *
11 mo.	2 days	3	15,000	8.7	21	23	21	Recovered
Years								
Age Group Over One Year								
6	1 day	5	100,000	8.2	6	50	19	Recovered
7	1 day	1	10,000	90 (0.2 iv)	5	6	3	Recovered
11	1½ days	8	105,600	5.5	21	69	15	Recovered
7	2 days	5	50,000	0.7	9	1	1	Recovered
8	2 days	4	70,000	24.3	21	49	16	Recovered
9	2-4 days	3	30,000	288	12	34	8	Recovered

* Patient died 9 months later.

Appelbaum, Nelson, and Albin [7] indicate reactions such as arachnoiditis, convulsions, and pyrexia in a small group. They suggest that cerebral irritation may be in part associated with large doses of the antibiotic intrathecally.

Cairns and others [11] found early in their study that with the use of impure preparations for intraventricular injections there were frequent mild reactions, such as patchy erythema of the skin, trunk, and limbs; generalized sweating, intermittent goose flesh, rise in pulse rate, and sometimes vomiting. All of these symptoms usually cleared within from 10 to 20 minutes. In Cairns' series, palsy and dysphagia were also observed after the intraventricular route. Waring and Smith [1] report a case of bilateral optic atrophy; and Appelbaum,[12] a case of transverse myelopathy following intrathecal penicillin.

The possible harmful effect of intrathecal medication was well understood even before the era of chemotherapy. This point has been repeatedly emphasized by Hoyne, who demonstrated that meningococcic meningitis may be even more effectively treated without intra-

8. Reuling, J. R., and Cramer, C.: Intrathecal Penicillin, J. A. M. A. **134**: 16 (May 3) 1947.

9. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin: Note of Warning, J. A. M. A. **127**: 217 (Jan. 27) 1945.

10. Walker, E. A.; Johnson, H. C., and Kollros, J. J.: Penicillin Convulsions, Surg., Gynec. & Obst. **81**: 692, 1945. Neyman, C. A., in discussion on Johnson, H. C.; Walker, E. A., and Case, T. J.: Effects of Penicillin on Central Nervous System, Arch. Neurol. & Psychiat. **54**: 160 (Aug.) 1945.

11. Cairns, H.; Duthie, E. S.; Lewin, W. S., and Smith, H. V.: Pneumococcal Meningitis Treated with Penicillin, Lancet **1**: 655, 1944.

12. Appelbaum, E., and Nelson, J.: Penicillin in the Treatment of Pneumococcic Meningitis, J. A. M. A. **128**: 778 (July 14) 1945.

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thecal medication [13] both as regards more rapid recovery and the development of fewer complications. Recently he has indicated that similar favorable results may be obtained in influenzal meningitis.[14] Rosenberg and Sylvester [15] have shown that during the period of infection of the meninges, the membranes may become permeable to the antibiotics, even though during health this relation may not hold. Such observations should favor the intramuscular mode of therapy and give support to withholding intrathecal therapy in many instances.

Many cases of residual spasticity and mental deficiency in the cured cases of meningitis using intrathecal therapy have been reported.[16] Some of these residua may be in part attributed to the disease, as it is characterized by a more abundant fibrin exudation than other varieties of acute bacterial meningitis. The tendency to adhesive arachnoiditis in pneumococcic meningitis is well known. Because of this subarachnoid block and the resulting hydrocephalus, relapse of the infection is not an uncommon sequela.

Only one of our patients, Case 6, a premature infant weighing under 9 lb. (4 kg.) at 4 mo. of age, had a relapse. This infant had seven intrathecal injections of penicillin, and for three days of this period the patient appeared clinically cured. The cultures were negative, the spinal fluid chemistry was normal, and the cell count was below 40 cells. Four days after discontinuance of intrathecal therapy, pneumococci were again grown from the spinal fluid, and a fall in spinal fluid sugar and an increase in spinal fluid cells were noted, together with a recurrence of signs and symptoms suggesting meningitis. Treatment was reinstituted immediately. A focus for the relapse was discovered in the right mastoid. Antrotomy on the right was effective in removing the focus, and prompt recovery followed.

It would appear from both a study of the cases reported in the literature and the observations of Hoyne [14] that a contributing factor to the severity of the sequelae is the amount of intrathecal therapy in terms of the number of intraspinal injections and total dosage of the antibiotic. However, since the severely ill patients receive more intense therapy, conclusions are difficult as regards the amount of therapy. Certainly patients seen early in the disease might best be treated with intensive intramuscular penicillin, and perhaps intravenous penicillin as well, together with sulfonamides without intrathecal therapy. In support of this argument is the recent report of Dowling, Sweet, and co-workers [17] on 21 patients, children and adults with pneumococcic meningitis, with a recovery of 13 (62%). Eighteen of these 21 patients were treated without intrathecal penicillin, the antibiotic being given in large amounts intramuscularly. In these cases the spinal fluid level of penicillin eight hours after intramuscular medication ranged from .08 to 1.25 units per cubic centimeter.

A statistical comparison of the fatality rate of patients reported in the literature treated with penicillin by the intramuscular route alone as compared with combined routes, intramuscular and intrathecal, is 31.4% and 20.8%, respectively.[18] When corrected for fatalities occurring within the first 24 hr. of treatment, there is no significant difference in the two groups. The insistence on the necessity for intrathecal penicillin therapy is not warranted by these figures. It may be that the severely ill patients are more likely to be treated with intrathecal medication, and thus the group with intramuscular therapy alone may contain more moderately and mildly ill patients. It is our opinion that intrathecal therapy is indicated when the factors influencing prognosis are unfavorable.

It is generally agreed that the younger the infant, the less favorable the prognosis becomes, and that recovery in newborn infants is unusual. In 1945 Hogg and Bradley [19] reported the recovery of one patient with pneumococcic meningitis in the neonatal period treated with sulfadiazine alone. They reviewed the literature and found in 28 cases only two other recoveries, described by Ravenel [20] and Uhr,[21] both cases having been treated by repeated spinal drainage only, thus giving a total of three recoveries in the newborn period. Ravenel's case of pneumococcic meningitis was diagnosed entirely from the finding on smears of gram-positive organisms in the spinal fluid; the diagnosis was not confirmed by cultures. Pneumococci were cultured from the spinal fluid in the case reported by Uhr in 1929. Recovery of a newborn infant with pneumococcic meningitis using penicillin was reported in 1947 by Cohlan and Solomon.[22] This 25-day-old infant was treated with penicillin, intrathecally on four occasions, intravenously for four days, and intramuscularly over a long period of time, together with sulfadiazine. The infant was cured and had no residua when seen at 20 mo. of age. Two separate reports in the French literature in 1947 each described newborn infants, 2 days [23] and 7 days [24] of age, who recovered promptly following combined sulfonamide and penicillin therapy, the latter drug given both intrathecally and intramuscularly. We are adding a seventh case of recovery from pneumococcic meningitis in the newborn period, an infant who although only 4 weeks of age was cured with only 4,000 units of intrathecal penicillin, the antibiotic being given intramuscularly in large amounts as well. A follow-up one year later revealed a normal infant.

A final comment concerning the changed picture in pneumococcic meningitis since the introduction of the

13. Hoyne, A. L.: Meningococcic Meningitis: Importance of Intravenous Therapy, Illinois M. J. **68**: 307 (Oct.) 1935; Treatment of Meningococcic Meningitis without Intraspinal Therapy, Nebraska M. J. **21**: 321 (Sept.) 1936.

14. Hoyne, A. L., and Brown, R. H.: Intrathecal Therapy Not Required for H. Influenzae Meningitis, J. A. M. A. **136**: 597 (Feb. 28) 1948. Hoyne, A. L.: Complications of Acute Pyogenic Meningitides, Am. J. Dis. Child. **75**: 741 (May) 1948; Advances in the Treatment of Meningitis, J. Pediat. **19**: 778, 1941.

15. Rosenberg, D. H., and Sylvester, J. C.: Excretion of Penicillin in Spinal Fluid in Meningitis, Science **100**: 132, 1944.

16. Warring and Smith.[3] Ross and Burke.[2] Hutchins and Davies.[6]

17. Dowling, H. F.; Sweet, L. K.; Robinson, J. A.; Zellers, W. W., and Hirsh, H. L.: The Treatment of Pneumococcic Meningitis with Massive Doses of Systemic Penicillin, Am. J. M. Sc. **217**: 149, 1949.

18. Table 2 in reprints. Some reports could not be used for this comparison because they contained no division by age group with reference to therapy.

19. Hogg, P., and Bradley, C. D.: Pneumococcic Meningitis in the Newborn, J. Pediat. **26**: 406, 1945.

20. Ravenel, S. F.: Spontaneous Recovery from Pneumococcus Meningitis: Report of a Case in a Newborn Infant, South. M. J. **29**: 86, 1936.

21. Uhr, J. S.: Pneumococcus Meningitis, Arch. Pediat. **46**: 121, 1929.

22. Cohlan, S. Q., and Solomon, N. H.: Pneumococcic Meningitis, Am. J. Dis. Child. **74**: 481 (Oct.) 1947.

23. Verger, P.; Martin, C., and Martin: Méningite à pneumocoques chez un nouveau-né de 2 jours: Guérison sans séquelles par la pénicilline, J. de méd. de Bordeaux **124**: 428, 1947.

24. Boursier, R., and Ducassou, J. L.: Méningite à pneumocoques chez un nouveau-né: Guérison par la Pénicilline-therapie; J. de méd. de Bordeaux **124**: 583, 1947.

sulfonamides relates to the pathogenesis of the disease. One of us has been interested in the pneumonias of childhood for many years and has observed that the development of pneumococcic meningitis as a late and terminal complication of pneumococcic pneumonia was not uncommon. Such a sequence of events has not been observed on this service throughout the period of study here reported. Only two of the 15 patients in this series of cases had pneumonia, both instances of which were mild and apparently not the foci for the meningitis.

SUMMARY

1. Fifteen patients from 4 weeks to 11 yr. of age who had pneumococcic meningitis are reported. Fourteen recovered, and one infant who was moribund on admission died 32 hr. later.

2. In a 10-mo.-old infant admitted after five days of illness severe hydrocephalus developed and he died nine months later. A follow-up study on 11 patients made from six months to five years after the infection showed no residua attributable to the meningitis.

3. One patient recovered without the use of intrathecal medication, and a second had only negligible amounts intrathecally; three others had only one intrathecal injection.

4. Recovery of an infant 4 weeks of age is reported, the seventh newborn infant reported in the literature as recovering after pneumococcic meningitis.

5. All patients received penicillin intramuscularly, in fairly large amounts, and sulfonamides orally. Two patients were given penicillin intravenously, also.

6. The disadvantages of intrathecal therapy are discussed.

CONCLUSIONS

Pneumococcic meningitis is no longer a highly fatal disease. A composite study of all cases in infants and children using sulfonamides and penicillin systemically with or without intrathecal therapy gives a recovery rate of 81.0%. Early diagnosis and age of the patient are important prognostic factors.

In view of the clinical experiences herein described, as well as experimental evidence, it would appear that intrathecal therapy of pneumococcic meningitis is not always a necessity. The dangers of this therapy should be fully appreciated. It may be indicated in the treatment of the desperately ill patients and those seen late in the disease. Repeated intrathecal injections should be used in selected cases only. As a result of our studies, we would suggest that every effort should be made to curtail, if not to abandon, intrathecal medication in the treatment of pneumococcic meningitis.

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REACTION TO TETRACAINE (PONTOCAINE®) USED AS TOPICAL ANESTHETIC IN BRONCHOSCOPY

STUDY OF 1,000 CASES

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The distinct increase in definitive surgical operations for intrathoracic diseases and lesions during the past two decades has caused an even greater increase in the incidence of diagnostic procedures to confirm or to help rule out the presence of pathologic processes within the chest. As the mortality and morbidity following thoracic surgical procedures have decreased and inversely the cures and good results have increased, it has been extremely important and of universal interest that untoward reactions, morbidity, or mortality attendant on diagnostic procedures be reduced to an absolute minimum.

One of the most distressing and sometimes fatal [1] complications of endoscopic procedures has been the so-called "anesthetic reaction." In discussions with our colleagues, it has been evident that there has been a decided difference in opinion regarding the incidence and severity of the anesthetic reactions, as well as the anesthetic agent of choice. The opinions voiced have varied from the thought that endoscopic work should be a casual office procedure to the view that topical anesthetics should be used only in a hospital where facilities for artificial respiration and intravenous medication are immediately available. A review of the literature has revealed a similar diversity of opinion regarding the occurrence of anesthetic reactions and the role of the particular anesthetic agent in the production of these reactions. The reactions in general have been inadequately described.

This diversity of opinion and an unfortunate previous experience prompted the report of this study. Tetracaine (pontocaine®) hydrochloride was chosen as the anesthetic agent first to be studied because it had been proved to be efficient and widely used, although it is one of the

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. (*a*) Hansen, F. M., Jr., and Stealy, C. L.: Sudden Death Following the Use of Pontocaine as a Gargle Anesthetic for Gastroscopic Examination, Rev. Gastroenterol. **10**: 212-213 (July-Aug.) 1943. (*b*) Pfeiffer, R. L.: Hypersensitivity to Pontocaine: Report of Case, Arch. Ophth. **18**: 62-64 (July) 1937. (*c*) Phillips, F. J.; Congleton, V. L., and Tuttle, W.: Pontocaine Hydrochloride Reaction Relieved by Dial, Anesth. & Analg. **20**: 233-234 (July-Aug.) 1941. (*d*) Richards, R.: A Note on Causation of Sudden Death, Brit. M. J. **2**: 51-53 (July 12) 1947. (*e*) Schindler, R.: Results of Questionnaire on Fatalities in Gastroscopy, Am. J. Digest. Dis. **7**: 293-295 (July) 1940. (*f*) Thomas, J. W., and Fenton, M. M.: Fatalities and Constitutional Reactions Following the Use of Pontocaine, J. Allergy **14**: 145-159 (Jan.) 1943.

more controversial [2] of the topical anesthetics. In order to assess the effect of tetracaine hydrochloride, 1,000 consecutive diagnostic bronchoscopies on adults were studied. These procedures were performed on 947 patients from January, 1947 to December, 1949. The material used for the anesthesia was commercially prepared 2% topical tetracaine solution.

A number of methods have been utilized to produce anesthesia for endoscopic procedures, and recently a series of articles have described a variety of methods that are in use today.[3] Most of these techniques, however, have employed some form of spray or atomization, and because of rather frequent reactions and one death which we noted in a previous series of cases following spray application to the pharynx, this form of anesthetization was not used for this group of patients. In addition, it has been our opinion that the amount of absorption of the anesthetic agent was most difficult to judge following the use of spray, atomization, or nebulization.

ANESTHETIC PROCEDURE

The anesthetic procedure utilized was as follows: Preoperatively the patient receives 50 mg. of meperidine (demerol®) hydrochloride one-half hour prior to the administration of the anesthetic, and 2 grains (120 mg.) of phenobarbital (luminal®) sodium are given by hypodermic injection three and one hours respectively, prior to endoscopy. Ten cubic centimeters of 2% tetracaine solution is then poured into a sterile medicine glass. One cubic centimeter of this is aspirated into a 2 cc. Luer-Lok syringe through an attached laryngeal cannula. Cotton pledgets held in grasping forceps are then dipped into the remaining solution and pressed dry against the side of the medicine glass. The pledgets are placed successively between the faucial pillars, in each pyriform sinus, and held in each of the four locations for about one minute. Then 1 cc. of solution is placed in the trachea in two doses under visual guidance with use of a laryngeal mirror. This method has been efficient in production of satisfactory anesthesia in all these cases. The definite amount of anesthetic used has been difficult to determine, but by gravimetric measurements it was noted that an average of 1½ to 2 cc. of solution was utilized for the anesthesia. These measurements have been admittedly inaccurate because of probable absorption of saliva on the pledgets, as well as the expectoration of some of the anesthetic injected into the trachea, but in general it can be said that 30 to 40 mg. of tetracaine hydrochloride has been used in production of anesthesia for most of these cases.

METHOD AND RESULTS OF STUDY

All the patients enumerated have been studied by careful preoperative evaluation, including a history, an assessment of the general conditions, diagnosis or probable diagnosis; complete physical examination, including blood pressure determination, pulse, and respiratory rate, and a superficial neurological check of the eyes and extremities by a resident member of the surgical or anesthesia service. One hundred consecutive patients were studied by serial blood pressure, pulse, and respiratory rate determinations at five minute intervals, before, during, and after anesthesia. The remainder of the group were studied preoperatively as described, and with the appearance of any untoward reaction, the patient was immediately restudied by a specially trained team while the patient was being observed or treated. This was continued in the postreaction period.

There were 19 anesthetic reactions noted in this series of patients. Twelve of these were classified as minor, and seven as severe. The reactions were considered severe when convulsions or severe respiratory signs appeared, and minor when the reaction did not progress to the signs mentioned above.

The pattern of the minor reaction was essentially the same for all the patients in whom it occurred. After the application of the fourth pledget (in two) or after the first tracheal instillation (in five) and the second tracheal instillation (in five), the patient complained of weakness or began to show a syncopal type of reaction. The pupils were noted to dilate, the skin color became pale or gray, and the patient usually fainted. At this time the blood pressure fell precipitously in all these patients, the average reading being 70 systolic, 50 diastolic. The pulse became thready, and the pulse rate was usually noted to increase, although this was variable. In nine patients the pulse rate was counted at 96 to 140 beats per minute, and in three the pulse rate fell below 80 beats per minute. In one patient the pulse rate dropped to 40 beats a minute, and the heart rate on auscultation was found to be the same.

When this type of reaction occurred, the patient was immediately placed supine on the floor or on an operating table, and equipment was placed in readiness for intravenous medication and artificial respiration with oxygen. If twitchings of the face or hands were noted, or if the reaction was not alleviated within three minutes, the patient was given 5 cc. of 2½% thiopental (pentothal®)) sodium solution, and oxygen was given by anesthetic machine and mask. Three of these patients were given intravenously thiopental sodium because of the appearance of clonic movements of the fingers. Bronchoscopy was performed on all the patients soon after subsidence of the syncopal reaction and the establishment of a near normal blood pressure, or while they were anesthetized with the thiopental sodium solution. There were no untoward sequelae noted in any of these patients, and the blood pressure and pulse rate determinations postoperatively were essentially the same as the preoperative values.

All the patients in whom these minor reactions occurred were men. Their ages varied from 21 to 65. The

2. (*a*) Harken, D. E., and Salzberg, A. M.: Transtracheal Anesthesia for Bronchoscopy, New England J. Med. **239**: 383-385 (Sept. 9) 1948. (*b*) Lundy, J. S.: Clinical Anesthesia. A Manual of Clinical Anesthesiology, Philadelphia, W. B. Saunders Company, 1942. (*c*) Seevers, M. H., in discussion on Symposium: Anesthesia in Otolaryngologic Surgery, Tr. Am. Acad. Ophth. **53**: 320-321 (March-April) 1949.

3. Benedict, E. B.: Medical Progress: Endoscopy, New England J. Med. **226**: 449-455 (March 12, 1942); ibid. **228**: 253-258 (Feb. 25) 1943. Corabelli, A. A.: Laryngo-Tracheo-Bronchial Anesthesia for Bronchoscopy and Bronchography with Pontocaine, Dis. of Chest **15**: 532-547 (May) 1949. Harken and Salzberg.[2a] Imperatori, C. J., and Burman, H. J.: Diseases of the Nose, and Throat, ed. 3, Philadelphia, J. P. Lippincott Company, 1947. Jackson, C., and Jackson, C. L.: Diseases of the Nose, Throat, and Ear, Including Bronchoscopy and Esophagoscopy, Philadelphia, W. B. Saunders Company, 1946. Lierle, D. M.: Symposium: Anesthesia in Otolaryngologic Surgery; Topical and Infiltration Anesthesia, Tr. Am. Acad. Ophth. **53**: 288-293 (March-April) 1949. Miller, J. B.; Mann, F., and Abramson, H. A.: A Method for Topical Anesthesia by Nebulization of Local Anesthetics, Dis. of Chest **16**: 408-419 (Oct.) 1949. Titche, L. L.: Anesthesia in Tracheo-Bronchial Procedures, Dis. of Chest **13**: 452-455 (Sept.-Oct.) 1947.

diagnoses, presumptive or proved, of the underlying chest condition were tuberculosis in seven, bronchogenic carcinoma in two, bronchiectasis in two, and chronic asthma in one. In none of the patients was a deleterious effect of the anesthetic reaction noted on the primary disease. Repeat bronchoscopy with tetracaine hydrochloride anesthesia was done on three of these patients with tuberculosis, and no untoward results were noted; one of this latter group had received thiopental sodium because of finger twitchings at the time of his initial bronchoscopy.

Of the seven severe reactions, six were of the convulsive type, and one was a pronounced bronchospasm with status asthmaticus. The consulsive reactions were all essentially the same and varied only in their rapidity of development and intensity of the convulsions. An appreciation of these reactions can best be gained by a consideration of the individual patients in whom they were noted, and of whom a brief description follows.

REPORT OF CASES

Case 1.—The patient was a white man, 56, on whom bronchoscopy was performed on Aug. 12, 1947, because of an undiagnosed lesion in the right upper lung field. The patient was anesthetized in the manner described above, and he was transferred from an anesthesia chair to the bronchoscopy table. At the time he was placed on the table, he stated that he felt weak and somewhat lightheaded. Examination of the patient's pupils at this time revealed that they were moderately dilated and they appeared fixed. The patient was placed supine on the operating table, and his blood pressure was taken and revealed a tension of 150 systolic over 90 diastolic. This was an increase over his preoperative level, which had been 130/80. The pulse rate had increased from a preoperative level of 92 to 110. As the patient was being studied, it was noted that twitchings were occurring in the fingers of both hands. These rapidly progressed to clonic movements of both arms, and the feet were beginning to be involved in these clonic movements. A needle was placed in the left antecubital vein and 5 cc. of a 2½% solution of thiopental sodium was immediately administered. The patient was given oxygen by means of an anesthetic machine and mask. At no time was there any distinct change in the character of the patient's respiration or in the depth of respiration. There was a complete cessation of the clonic movements of the arms and feet in about 30 sec., and it was noted after three minutes that the blood pressure had decreased to 140/80. The pulse rate however remained at the level of 110 beats per minute. The patient was given an additional 5 cc. of 2½% thiopental sodium slowly, and the originally scheduled bronchoscopy was carried out.

The patient was observed postoperatively, and there were no untoward results noted in this patient's pulmonary disease or in his general condition. The blood pressure gradually fell to the preoperative level, as did the pulse and the respiratory rate.

Case 2.—A male veteran, 30, had a bronchoscopy performed because of far advanced, fibrocavitary tuberculosis of the left lung and suspected endobronchial tuberculosis. On Jan. 10, 1948, after the application of the fourth moistened pledget as described above, the patient was noted to have dilated pupils, and he did not respond to questions; he gradually slumped forward in the chair in which he was sitting for anesthetization. He was gently placed on the floor, and at this time the pulse rate was 102 beats per minute and the blood pressure was 90/60 compared to a preoperative pulse rate of 84 and a blood pressure level of 120/80. Twitching movements of the fingers were noted, which rapidly increased to clonic convulsive movements involving the arms, legs, and face, and his body became rigid. During this period the blood pressure rose to 140/90. At the onset of the finger twitchings, a needle was placed in the left antecubital vein, and an anesthesia mask was applied tightly to the face. Oxygen was administered, and with the onset of clonic convulsions, 10 cc. of 2½% solution of thiopental sodium was given intravenously. The convulsive state gradually disappeared, and at no time was there obvious interference with the respiratory effort or any changes in the cardiac beat except an increase in the rate. The patient was given an additional 5 cc. of the thiopental sodium solution. He was then transferred to the operating table, and bronchoscopy was performed with the patient asleep. There were no untoward results postoperatively, and two subsequent bronchoscopies were performed, 4 and 10% cocaine anesthesia being used, without ill effects.

Case 3.—Bronchoscopy was done on a white female nurse, 41, because of chronic, moderately advanced, fibrocavitary tuberculosis of the right upper lobe on May 3, 1948. After application of four moistened pledgets to the pharynx and pyriform sinuses and instillation of ½ cc. of solution in the trachea as described above, the following signs were noted within the course of about two minutes: the pupils became widely dilated; the patient did not respond to a question; twitching movements of the fingers rapidly progressed to convulsive movements of the facial muscles; the entire body was quickly thrown into a tonic and clonic convulsive state, and she assumed the position of opisthotonos. The respirations ceased, the patient became extremely cyanotic, and no pulse, blood pressure or heart beat could be obtained. At the onset of this reaction, 5 cc. of 2½% thiopental sodium was injected into the antecubital vein, and simultaneously artificial respiration was begun by means of an anesthesia machine, a tight fitting face mask and a rebreathing bag being used. The convulsive state gradually subsided, and the patient's color returned to normal. A heart beat became audible in about three minutes, and the peripheral pulse became palpable at this time. A blood pressure of 80/40 was obtained. The pulse gradually returned to normal in about five minutes, and the blood pressure rose to 100/80. Spontaneous respirations were resumed in about 15 minutes, and the patient, although asleep, appeared to be normal. Bronchoscopy was thereupon performed with no untoward results, and the patient was returned to her room in good condition. The patient was closely observed for three hours, and there were no abnormal variations of the pulse, respirations, or blood pressure. A later review of the patient revealed no untoward effect on the lung disease or on the cerebral function, although she complained of a severe headache for about 12 hours after she had responded.

Case 4.—A white man, 25, had bronchoscopy performed on Sept. 14, 1948, because of moderately advanced, unilateral, fibrocavitary tuberculosis. Following the application of the fourth pledget and as the larynx was being visualized for intratracheal instillation of the anesthetic agent, twitching movements of the lips and face were noted. These rapidly increased to clonic and tonic convulsions of the extremities and torso, and the patient became cyanotic. These events occurred too rapidly to allow studies of the pulse and blood pressure. The patient was placed on the operating table and 10 cc. of 2½% thiopental sodium solution was injected rapidly into the left antecubital vein. Oxygen was given by means of a tight fitting face mask and anesthesia machine. The convulsion ceased in about two minutes; the respirations were normal, and the tidal exchange volume had returned to normal by this time. The patient's pulse, although rapid (106 beats per minute), was regular. The blood pressure was 110/80, which was very similar to a preoperative determination. Bronchoscopy was done on the patient while he was anesthetized, and an active endobronchial tuberculosis was noted. No untoward effect of the convulsive reaction was noted. Two subsequent bronchoscopies were performed on the patient at this hospital without incidence. Cocaine was used as the anesthetic agent on one occasion, and tetracaine hydrochloride was utilized as the anesthetic agent in the other.

Case 5.—A white man, 52, was to have bronchoscopy performed on Oct. 19, 1948, because of a chronic cough and an undiagnosed hilar lesion of the left lung. After anesthetization of the pharynx and the instillation of ½ cc. in the trachea, an audible wheeze was noted, which was thought to be due to upper respiratory tract spasm. After instillation of a second ½ cc. of anesthetic solution, however, the patient entered a severe status asthmaticus. The patient's respirations became extremely labored, and this was especially noted in the expiratory phase. A deep cyanosis rapidly developed. The patient's pulse rate rose from a preoperative rate of 98 beats per minute to 126. The blood pressure rose from 120 systolic and 80 diastolic to

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180/110. He became very apprehensive, and although preoperatively he had been given sedatives, he showed a hypomanic response.

Epinephrine was given subcutaneously repeatedly without apparent effect, and intravenous administration of aminophylline produced no improvement. He was given oxygen by a face mask and later helium and oxygen with a slight decrease of the cyanosis. During the ensuing 36 hours, the patient's condition remained about the same except for a gradual development of bilateral scattered atelectatic areas and rales at the bases. For this reason, bronchoscopy was performed with the patient under general ether anesthesia. No localized endobronchial lesion was observed, although the patient presented a chronic, asthmatic type of bronchitis. After this procedure the patient improved rapidly, and the lung fields were clear to physical and radiologic examination within three days.

CASE 6.—A white man, 52, was anesthetized for bronchoscopy on Dec. 14, 1948, as part of an examination of a cystic lesion of the left lower lung. After the second instillation of ½ cc. of 2% tetracaine hydrochloride solution into the trachea, the patient complained of feeling very weak and lightheaded, and it was noted that his pupils were becoming dilated. He was immediately placed supine on an operating table, and his pulse rate was noted to have increased from 72 to 130 beats per minute, while his blood pressure had dropped from 120/80 to 90/40. After about one minute, twitching movements of the fingers were noted, and the patient was given oxygen by an anesthetic mask, a needle being placed in the left antecubital vein. Because of technical difficulties, no thiopental sodium was given for about four minutes, and during this time clonic convulsive movements of the face and extremities developed. During this convulsive period the blood pressure determination rose to 150/90, and the pulse rate was counted as 120 beats per minute. The convulsive movements stopped before the anesthesia could be given intravenously, but the patient appeared to be in a tense tonic state so that 8 cc. of a 2½% thiopental sodium solution was injected, with complete relaxation of the patient. Bronchoscopy was then performed with the patient under the anesthesia, and his recovery was uneventful. The blood pressure and pulse returned to preoperative values after the patient reacted, and there was no untoward effect on his general condition or on the pulmonary situation.

CASE 7.—A white man, 58, was anesthetized for bronchoscopy on Feb. 7, 1949. The patient was known to have pulmonary tuberculosis, and an endobronchial lesion had been suspected from clinical studies. The patient had been anesthetized in the usual manner, and a bronchoscope had been passed after the patient was placed in appropriate position. As the bronchi were being inspected, an assistant noted the appearance of twitching movements of the hands and forearms. The instrument was withdrawn, and arrangements were made for the intravenous administration of thiopental sodium and for a high concentration of oxygen by means of an anesthetic mask. During these preparations, the twitching movements became convulsive in character, and they involved the face and extremities. There was an apparent respiratory arrest during this period, but no appreciable change in the pulse rate or volume or in the heart rate was noted. After the injection of 5 cc. of 2½% thiopental sodium solution into the left antecubital vein, the convulsive movements ceased, and the patient resumed normal respiratory movements in about 30 sec. He was given an additional 3 cc. of solution intravenously, although no further convulsive movements were noted. The patient responded in about 20 minutes, and no untoward general or pulmonary complications were noted following this convulsive reaction.

COMMENT

The toxicity of the commonly used agents for surface anesthesia has long been recognized, and comparisons of the relative dangers of the drugs have been made by a number of workers.[4] Reports of the clinical incidence of these reactions and of the physiologic effect on patients have, however, been few in number. The fact that the danger of an anesthetic reaction may be very real was made clear to us by the death of one patient, which we had attributed directly to an anesthetic reaction, and which occurred prior to the study of this series of patients.

The fact that these reactions can be prevented and controlled by barbiturates [5] has been a most important factor in our continued use of the local anesthetic drugs. We feel that were it not for the use of considerable preoperative medication, the reaction rates from this agent might be higher, and we are certain that the intravenous use of thiopental sodium has prevented a fatal outcome in some of the cases herein reported.

The use of the barbiturates alone does not constitute a sufficient safety mechanism, however, and we believe that facilities for oxygen administration and particularly for artificial respiration must be immediately available. It is possible that cardiac resuscitation might also be indicated, and for that reason, a surgical setup would be essential. In regard to cardiac arrest, it has been our experience that some apparent instances of this complication have not been real, and, therefore, we would advise conservatism in the performance of thoracotomy for patients having these anesthetic reactions.

Tetracaine hydrochloride as an anesthetic has been excellent, and we have been impressed by its quick action and the consequent short period of time required for the anesthetization procedure. We believe that from a practical standpoint, however, the potential dangers of this drug must be recognized, but we do not mean to condemn the agent for this reason any more than the other local anesthetic drugs can be criticized, because toxic reactions from their use have been seen and reported. By the use of small doses, as pointed out by the company marketing tetracaine hydrochloride, and by the proper preoperative medication, the incidence of reactions should be small. In addition, the prompt recognition and treatment of reactions should prevent serious complications.

The incidence of reactions reported in this series has been much higher than that previously noted, and we have attempted to explain this by a careful survey of the patients in whom the reactions were noted. Unfortunately, there have been no significant factors found that might account for these figures. The age and physical condition of the patient have not been unusual when compared to the group as a whole; the disease process and the presence of such signs as hemoptysis, wheezing, and allergic manifestations have not been different from the larger group of patients in whom no reactions occurred.

In the group of 100 consecutive patients who were studied routinely by serial determinations of the blood pressure, pulse, and respiratory rate, there was a uniform response. The blood pressure showed a slight to moderate elevation of both systolic and diastolic levels, and this varied directly with the degree of coughing occasioned by the intratracheal instillation of the solution. In addition, there was a moderate elevation of the pulse and respiratory rate. It was our impression that these

4. Gomori, G.: Accidents of Local Anesthesia, Surg., Gynec. & Obst. **62**: 951-959 (June) 1936. Seevers.[2c]

5. Fraser, R. J., and Stringer, R. M.: Pentothal Sodium in Relation to the Toxic and Convulsive States, Canad. M. A. J. **62**: 249-252 (March) 1940. Phillips, Congleton, and Tuttle.[3c] Tuohy, E. B.: Practical Concepts in Anesthesia, Ohio State M. J. **43**: 148-153 (Feb.) 1947.

changes were independent of the anesthetic and were more dependent on the patient's apprehension and his response to the procedures. These changes usually lasted during bronchoscopy and for an average of one-half hour after the procedure. It is interesting that this vascular response was the opposite of that noted in the patients with minor reactions, and also in those with the severe reactions who were studied prior to the onset of convulsions or bronchospasm. The fact that the systemic effects of the anesthetic were generally negligible makes the explanation of the toxic reactions very difficult, except on the basis of some idiosyncrasy existing at that time. The fact that patients who had had reactions could be reanesthetized without event has further confused our attempts at explaining the mechanism involved.

SUMMARY

A study is reported of 1,000 consecutive bronchoscopies in 947 patients, with use of 2% topical tetracaine (pontocaine*) hydrochloride anesthesia, in whom there were 12 minor and seven severe toxic reactions attributed to the anesthetic agent. An attempt has been made to evaluate a few physiologic changes in patients anesthetized with tetracaine hydrochloride. We feel that tetracaine hydrochloride is an excellent agent for topical anesthesia, but that its danger must be appreciated. It should be used with caution in a hospital where adequate preoperative medication can be given and where all resuscitative measures are immediately available.

Veterans Administration Center.

ARTIFICIAL TRANSMISSION OF VIRAL HEPATITIS AMONG INTRAVENOUS DIACETYLMORPHINE ADDICTS

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During the past few years much attention has been focused on the epidemiology of virus hepatitis, especially the accidental transmission of the disease through parenteral infusions and inoculations. The infectiousness of even minute quantities of human blood or serum has been amply demonstrated.

The accidental dissemination of various infections among intravenous drug addicts is now a recognized fact. Of special interest are reports [1] on the artificial transmission of malaria, tetanus, and bacterial and mycotic endocarditis. To the best of our knowledge, there have been no references in the literature to the spread of hepatitis or other viral infections among these patients. Recently we had an opportunity of studying three cases of hepatitis among intravenous drug addicts. It is the purpose of this paper to record these cases and to draw attention to this mode of spread of hepatitis and to this additional hazard of narcotic addiction.

REPORT OF CASES

CASE 1.—C. G., a Negro man, 23, admitted to Beth David Hospital, May 21, 1951, complained of fatigue, abdominal discomfort, anorexia and vomiting of three weeks' duration, and yellow discoloration of the eyes, pale stools, and dark urine for the past week. He had been taking diacetylmorphine (heroin) intravenously for 18 mo. and had been sharing his hypodermic outfit with other addicts up to the time of his admission to the hospital. The patient had not received any other injection or inoculation for the past four years. Early in March, 1951, jaundice developed in a fellow addict, L. B., with whom the patient had shared injections up to Feb. 20, 1951, and he was admitted to another hospital. The patient's past history was irrelevant.

The patient was well nourished and did not appear particularly ill. However, the scleras and buccal mucous membrane were intensely jaundiced. The temperature was 100 F., the pulse rate 100, and the respiratory rate 22. The pupils were equal and reacted to light and in accommodation. The lungs were clear. The heart was normal. The blood pressure was 150 mm. of mercury systolic and 90 diastolic. There was no abdominal distention, but there was some tenderness on deep pressure over the right hypochondrium. The liver and spleen were not palpable. Both antecubital fossae and the forearms showed scarring and pigmentation along the course of the veins. Except for diminished patellar reflexes, the reflexes were normal.

The red blood cell count showed 4,240,000 cells, with 90% hemoglobin. The white blood cell count was 5,050, with 50% polymorphonuclears, 41% lymphocytes and 9% monocytes. Urinalysis showed a specific gravity of 1.017, an occasional white blood cell, a trace of bile and urobilinogen, but no sugar or albumin. The erythrocyte sedimentation rate was 11 mm. in 15 min. Both the Wassermann and Mazzini tests were negative. The icteric index was 66, the cephalin flocculation 3+, and the alkaline phosphatase 5.51 units. The serum albumin was 4.5 and the globulin 3.8 gm. per 100 cc. The value for blood urea was 13 mg. and for sugar 133 mg. per 100 cc. A roentgenogram of the chest showed the heart and lungs to be normal.

Treatment consisted of bed rest, a high-carbohydrate and high-protein diet, and daily administration of liver extract parenterally. Diacetylmorphine was not given. The clinical course was uneventful, with gradual return of the patient's appetite and subsidence of the abdominal discomfort. The jaundice receded slowly. A sulfobromophthalein (bromsulphalein*) sodium test done on June 7 showed 40% retention of dye after 45 min. The same test repeated two weeks later showed only 2% retention. At about the same time the cephalin flocculation test became negative. When the patient was discharged from the hospital on July 2, 1951, he showed no jaundice and was in excellent condition. The icteric index taken the same day was 17.

From the Medical Services of Beth David and Sydenham Hospitals.

1. Appelbaum, E., and Gelfand, B. B.: The Artificial Transmission of Malaria among Intravenous Diacetylmorphine Addicts: Preliminary Note on the Use of Atabrine in Malaria, J. A. M. A. **102**: 1664-1670 (May 19) 1934. Helpern, M.: Epidemic of Fatal Æstivo-Autumnal Malaria among Drug Addicts in New York City Transmitted by Common Use of Hypodermic Syringe, Am. J. Surg. **26**: 111-123 (Oct.) 1934. Doane, J. C.: Tetanus as a Complication in Drug Inebriety, J. A. M. A. **82**: 1105-1106 (April 5) 1924. Schoenbach, E. B., and Spingarn, C. L.: Inoculation Malaria and Drug Addiction, J. Mt. Sinai Hosp. **8**: 998-1004, 1942. Hussey, H. H.; Keliher, T. F.; Schaefer, B. F., and Walsh, B. J.: Septicemia and Bacterial Endocarditis Resulting from Heroin Addiction: Report of 5 Cases, J. A. M. A. **126**: 535-538 (Oct. 28) 1944. Wilhelm, F.; Hirsh, H. L.; Hussey, H. H., and Dowling, H. F.: The Treatment of Acute Bacterial Endocarditis with Penicillin, Ann. Int. Med. **26**: 221-230, 1947. Joachim, H., and Polayes, S. H.: Subacute Endocarditis and Systemic Mycosis (Monilia), J. A. M. A. **115**: 205-208 (July 20) 1940. Wikler, A.; Williams, E. G.; Douglass, E. D.; Emmons, C. W., and Dunn, R. C.: Mycotic Endocarditis: Report of a Case, ibid. **119**: 333-336 (May 23) 1942.

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In this case the diagnosis of hepatitis was definitely established by the clinical picture and laboratory data. It is important to note that this patient shared the hypodermic outfit with addict L. B., who was treated for hepatitis in another hospital. The last time that these two addicts shared injections was about 70 days prior to the onset of the present illness in patient C. G. The accidental transfer of hepatitis from addict L. B. to our patient is a reasonable assumption, although the possibility that both patients acquired the disease from a common source cannot be excluded. If L. B. was the source of our patient's infection, then the minimum incubation period was 70 days. This would favor a diagnosis of homologous serum hepatitis.

CASE 2.—C. B., a Negro girl, 16, was admitted to Sydenham Hospital, June 7, 1951, with the complaint of yellowish discoloration of the eyes, a symptom to which her attention was directed by friends on the same day. She had noticed that her urine was getting darker than usual for the past three weeks. There was no history of nausea, vomiting, or abdominal distress. She had been taking diacetylmorphine intravenously for the past two months, sharing a hypodermic outfit with other addicts, one of whom was being treated for hepatitis in another hospital. There was no history of blood transfusion or any other parenteral inoculation.

The patient was well developed and did not appear acutely ill. The temperature was 99.6 F., the pulse rate 88, and the respiratory rate 20. The blood pressure was 115 mm. of mercury systolic and 65 diastolic. There was poor oral hygiene and coating of the tongue. The scleras were icteric. The lungs were clear. The heart was not enlarged, and the rhythm was regular. There was moderate enlargement and tenderness of the liver. The spleen was not felt. Scarring and pigmentation was seen over the veins of the forearms. Some of the veins appeared thickened and sclerosed. The reflexes were all normal.

The red blood cell count showed 4,610,000 cells, with 11 gm. of hemoglobin. The white blood cell count was 10,200, with 46% polymorphonuclears and 54% lymphocytes. Urinalysis showed a few white blood cells and numerous epithelial cells, but findings were otherwise normal. The blood urea was 5.4 mg., the sugar 127 mg., the phosphorus 3.6 mg., the cholesterol 282 mg. and the ester 146 mg. per 100 cc. The serum albumin was 3.6 gm. and the globulin 2.6 gm. per 100 cc. The icteric index was 41, and the van den Bergh showed an immediate reaction on the direct test and 3.5 mg. per 100 cc. on the indirect test. The cephalin flocculation was 4+ and the alkaline phosphatase 13.7 Bodansky units. The prothrombin time was 31 sec., and the urobilinogen was present in the urine in 1: 20 dilution. A sulfobromophthalein test done on June 13 showed a 40% retention in the serum 45 min. after injection of the dye. A roentgenogram of the thorax showed the heart and lungs to be normal.

The patient was treated with bed rest, a high-carbohydrate and high-protein diet, and also lipotropic agents, crude liver, and vitamins. Remarkable clinical improvement followed, with clearing of the jaundice and diminution in the size and tenderness of the liver. At the request of a probation officer, the patient was discharged from the hospital on June 20 and transferred to the House of the Good Shepherd.

In this case the clinical picture and course, combined with the laboratory data, warranted a diagnosis of hepatitis. The relationship of the patient's illness to narcotic addiction appears probable, since she had shared injections with an addict who was suffering from hepatitis. If the patient's statement that she had taken intravenous diacetylmorphine for only two months is correct, then the incubation period of her illness was comparatively short but may have been 60 days. The precise form of this patient's hepatitis is therefore a matter of speculation.

CASE 3.—W. H., a Negro man, 24, admitted to Beth David Hospital, June 21, 1951, complained of fatigue, lassitude, abdominal discomfort, and yellow discoloration of the eyes of one week's duration. He noticed at the same time that the stools were light-colored and the urine dark. He had been taking diacetylmorphine intravenously for the past five months and had been sharing his hypodermic outfit with other addicts. His last injection was on June 10. He had not received any other injection during the past year and had not been exposed to any intoxicating chemicals. He did not recall encountering any jaundice cases among his fellow addicts. Although he knew C. G. (case 1), he never shared injections with him. His past history was irrelevant.

The patient was well nourished and did not appear either acutely or chronically ill. The temperature was 99 F., the pulse rate 74, and the respiratory rate 18. The pupils were equal and reacted to light and in accommodation. The lungs were clear. The heart was not enlarged, and the rhythm was regular. The blood pressure was 103 mm. of mercury systolic and 60 diastolic. The abdomen was soft and not distended. There was slight tenderness on deep palpation below the right costal margin. The superficial veins of the forearms were thrombosed and scarred. All reflexes were normal.

The red blood cell count showed 4,810,000 cells, with 94% hemoglobin. The white blood cell count was 7,100, with 59% polymorphonuclears, 38% lymphocytes, and 3% eosinophils. Urinalysis showed a faint trace of albumin, eight to 10 white blood cells, and a trace of bile and urobilinogen. Both the Wassermann and Mazzini tests were negative. The cephalin flocculation test was 2+ and the alkaline phosphatase 5.1 units. The icteric index was 80. The serum albumin was 3.56 gm. and the globulin 3.83 gm. per 100 cc. The blood urea was 10 mg., the cholesterol 200 mg., and the ester 100 mg. per 100 cc. The stools appeared clay-colored. A sulfobromophthalein test revealed 40% dye retention after 45 min. A roentgenogram of the chest revealed the lungs and heart to be normal.

The patient was treated with bed rest, a high-carbohydrate and high-protein diet, and vitamins. Response to this regimen was prompt, and the clinical course to date has been very favorable. While the patient is still jaundiced, he is quite comfortable, and a sense of well-being has developed. The stools are no longer clay-colored. The patient is still under observation.

The clinical picture and course and the laboratory findings in this case are consistent with a diagnosis of hepatitis. There is no history of definite contact with another patient with hepatitits. However, the fact that the patient was an intravenous drug addict suggests very strongly that the hepatic infection was transmitted by means of a contaminated hypodermic outfit. In this case it is impossible to determine the incubation period or the precise form of viral hepatitis.

COMMENT

It is not within the scope of this paper to discuss the various aspects of hepatitis on which an extensive literature has been accumulated during the past few years. Suffice it to mention that the virus etiology of both infectious hepatitis and homologous serum jaundice is now an accepted fact. In the three cases reported herein, the history, clinical picture and course, and laboratory data leave no doubt as to the diagnosis of viral hepatitis. In case 1 the apparently long incubation period makes the diagnosis of homologous serum jaundice very likely. The precise form of hepatitis present in cases 2 and 3 is speculative.

As mentioned previously, the transmission of hepatitis through parenteral injections has been established. In this connection it may be pertinent to describe briefly the method of group injection practiced by the narcotic addicts. The drug used is almost invariably diacetylmorphine and is as a rule administered intravenously. The

addicts usually congregate in groups. The drug is put into a tablespoon, and tap water is added. The contents are then brought to a boiling point by using a candle or match flame. A small piece of cotton is put into the tablespoon, and the solution is drawn up through the cotton into a large medicine dropper. Strips of paper are wrapped around the tip of the dropper in order to fit the needle. After a tourniquet is applied to the arm, the needle is inserted into one of the antecubital veins. When the flow of blood into the eye dropper is observed, the tourniquet is released, and the solution is injected into the vein. The hypodermic outfit, known as "the works," is never sterilized and is passed around from one addict to another. It is obvious that this method lends itself to the transfer of infectious agents from one addict to another.

In our patients there can be little doubt that hepatitis was artificially induced in cases 1 and 2. In case 3 the relationship between the hepatitis and the injections is a reasonable assumption. It has also come to our attention that other intravenous drug addicts suffering from hepatitis have been admitted to several hospitals in the city during the past few months.

There is therefore sufficient evidence that a number of intravenous diacetylmorphine addicts have accidentally acquired viral hepatitis while sharing injections with other addicts who were afflicted with this disease. It is not unlikely that more cases of this type will soon be uncovered. Attention is thus directed to another hazard of narcotic addiction, namely, the transmission of a virus infection. The public health implications of this extraordinary manner of spreading hepatitis cannot therefore be overemphasized. This problem assumes particular importance at this time because of the recent exposure of the widespread existence of diacetylmorphine addiction, especially among adolescents.

SUMMARY

Three cases of viral hepatitis among intravenous diacetylmorphine (heroin) addicts have been reported. It was pointed out that transmission of the disease among these patients was very likely due to the communal use of hypodermic outfits. This extraordinary manner of spreading hepatitis focuses attention on another hazard of narcotic addiction and on an important public health problem.

ADDENDUM

Since this manuscript was submitted, additional information has become available. Hepatitis developed on or about July 10, 1951, in a fellow addict under observation in another hospital, with whom our patient, W. H. (case 3), had shared injections up to the end of April, 1951. Assuming that our patient was the source of this other addict's infection, the probable incubation period in the new case was approximately 70 days. This would favor a diagnosis of homologous serum hepatitis in both patients.

It may also be noted that clinical improvement in case 3 was progressive. The sulfobromophthalein retention on July 8 was 2%, and the icteric index on July 18 was 13. At the time of discharge on July 21 the patient was in excellent condition.

We should also like to record briefly an additional case of hepatitis in a diacetylmorphine addict which has since come under our care. On July 28, 1951, P. C., a Negro man, 26, was admitted to Beth David Hospital with the complaints of weakness, anorexia, nausea, vomiting, and jaundice of five days' duration. He had been taking diacetylmorphine intravenously for the past eight months and occasionally had shared his hypodermic equipment with other addicts. On examination the patient appeared acutely ill and asthenic. The temperature was 100 F., the pulse rate 84, and the respiratory rate 20. The blood pressure was 140 mm. of mercury systolic and 85 diastolic. The scleras and mucous membranes were icteric. The heart and lungs presented no abnormal findings. The liver was moderately enlarged and tender, and the spleen was palpable. Both forearms showed scarring and pigmentation along the course of the veins. The reflexes were all normal. The red blood cell count showed 4,100,000 cells, with 84% hemoglobin. The white blood cell count was 3,100, with 49% polymorphonuclears, 38% lymphocytes, 6% monocytes, and 7% eosinophils. The urine showed urobilinogen in 1:32 dilution but no bile. The icteric index was 53, the cephalin flocculation 2+, and the alkaline phosphatase 3.82 units. The blood urea was 13.8 mg., the cholesterol 245 mg., and the esters 125 mg. per 100 cc. A sulfobromophthalein test showed 45% dye retention after 45 min. Treatment consisted of bed rest, high protein and high carbohydrate diet, and the use of vitamins and lipotropic substances. Clinical improvement became apparent after several days of therapy. This patient is still under observation.

Since describing the above patients, one of us (E. A.) has observed four additional cases of hepatitis among drug addicts, indicating that the disease is spreading in this group.

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Psychiatry and Freud.—Freud shocked the world of science and of intellect in arguing and in demonstrating both the rationality of the irrational and the irrationality of the rational. The first of the two propositions was the less opposed; the second aroused frenzied resentment. It is this split with the formal rationalism of his age that distinguishes and separates Freud from his contemporaries in science and psychiatry. . . . It was the firm faith of the nineteenth century that "la raison a toujours raison, that memories and shadows were less important than the direct perception of the real world in the clear light of the day." These were the common assumptions of the rationalistic enlightened world. It is true that these assumptions were challenged and denied by a few isolated, "eccentric" thinkers—Carlyle, Dostoievski, Baudelaire, Tolstoi, Nietzsche. However, none of these was "a man of science," and hence none of them really challenged science. Such discomfiture as they caused to science could be neutralized by anatomizing them and exposing, as Max Nordau did, their "degeneracy." . . . Freud, unlike the other isolated and eccentric thinkers, was a man of science. Though many a Nordau tried it, Freud could not be anatomized or his "degeneracy" exhibited for the pleasure and profit of the intellectual pharisees. He stood forth an obdurate challenge to the naïve rationality of the nineteenth century, and he endures as such to this day. The antirationalism of Freud proffers some deep and challenging problems—in epistemology, in the dynamics of therapy, in esthetics and morals—problems which few have braved, but with which we must soon come to grips.—Iago Galdston, M.D., Psychiatry Without Freud, *A. M. A. Archives of Neurology and Psychiatry*, July, 1951.

PODOPHYLLUM RESIN IN TREATMENT OF TINEA CAPITIS

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In a preliminary report [1] evidence was submitted that a 0.2% ointment of podophyllum resin (podophyllin), in an aquaphor* (an oxycholesterol-petrolatum ointment base) or a polyethylene glycol (carbowax*) base, had a beneficial affect upon the course in several cases of tinea capitis. Further clinical trial of this medication, while producing results not quite up to earlier expectations, indicated that podophyllum resin was sometimes a useful agent in the treatment of this rather recalcitrant disease.

PRESENT INVESTIGATIONS

In every case the diagnosis was made both clinically and by the presence of fluorescence under the Wood light. It was further confirmed by microscopic examination of the hair and subsequent culture. Each patient was given the routine instructions for the treatment of tinea capitis and a supply of 0.2% podophyllum resin in carbowax* 1500 and each was instructed to apply the ointment twice daily, carefully avoiding contact with his eyes. Every patient was informed also of the possibility of an inflammatory reaction following continued use of the ointment. When this occurred, the patient was instructed to apply either boric acid compresses or boric acid ointment, depending upon the severity of the reaction. In three instances the parents neglected the reaction until heavy crusting resulted. In these cases treatment with podophyllum resin was discontinued, and 2% salicylic acid in cottonseed oil was applied under a cap. After subsidence of the inflammation the podophyllum resin ointment was reapplied. In these children the salve was applied only once a day. Our results are tabulated in table 1.

In all patients with tinea capitis cures were judged by the disappearance of subjective manifestations and the cutaneous lesions, the absence of fungi in slide preparations and cultures, and the absence of fluorescence under Wood light. If all these were absent on four consecutive weekly examinations, a patient was pronounced cured.

TABLE 1.—*Results of Treatment with Podophyllum Resin Ointment*

Organism	Cured			Improved			No Change			Spread While Under Treatment, Podophyllum Only	Lost	Total
	Podophyllum and X-Ray	Podophyllum Only	Total	Podophyllum and X-Ray	Podophyllum Only	Total	Podophyllum and X-Ray	Podophyllum Only	Total			
M. audouini	24	22	46	3	15	18	3	18	21	9	15	109
M. lanosum	0	7	7	0	1	1	0	0	0	0	0	8
T. sulfureum	1	0	1	0	0	0	0	0	0	0	0	1
Endothrix (unidentified)	0	1	1	0	0	0	0	0	0	0	0	1
T. crateriforme	1	0	1	0	0	0	0	0	0	0	0	1
T. violaceum	0	0	0	0	0	0	0	0	0	0	1	1
Total	26	30	56	3	16	19	3	18	21	9	16	121

x-ray epilation should be resorted to only after at least eight weeks of local treatment and lack of response to therapy. Table 3 illustrates the time required for cure with treatment combining x-ray epilation and subsequent application of podophyllum resin ointment.

CURE ACHIEVED IN TRICHOPHYTON (T.) SULFUREUM INFECTION

In addition to the above cases, in one case of widespread T. sulfureum infection cure was achieved in five and one-half months.

CURE ACHIEVED IN INFECTION DUE TO TRICHOPHYTON (T.) CRATERIFORME

In one case of a widespread infection due to T. crateriforme, a rather resistant type of infection, the lesions cleared in four months.

TIME REQUIRED FOR CURES AFTER LOCAL APPLICATION WITH PODOPHYLLUM RESIN OINTMENT

Of the 105 children followed up, cure was achieved in 30 with the local application of a 0.2% podophyllum resin in carbowax* 1500. This varied from two weeks to seven months. Table 2 illustrates the time required in various types of infections.

TIME REQUIRED FOR CURES WITH X-RAY EPILATION AND SUBSEQUENT APPLICATION OF PODOPHYLLUM RESIN OINTMENT

This group comprises children with widespread involvement of the scalp to whom local therapy with podophyllum resin was given for two months. Since in our previous experience in over 20% of our cases there was failure to clear up after x-ray epilation and subsequent antimycotic treatment, it was our conviction that

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COMMENT

From the results obtained it is obvious that podophyllum resin is as efficacious as many other drugs applied in the past. In addition to its antifungal activity, a mild inflammatory reaction is observed in some instances which, according to our estimation, is not only harmless but rather beneficial. A noteworthy feature of the podophyllum resin treatment is that the infected hair becomes loose and can easily be epilated manually. In widespread infections due to M. audouini this is particularly desirable, and it becomes very important that the medication have a high antifungal index. Comparing our results in tinea capitis caused by M. audouini with those obtained by Schwartz and associates [2] and Combes and associates,[3] we feel justified in our conclusions (table 4). Of 73 patients, 30 were cured (42.0%), 16 were improved (21.9%), 18 showed no change (24.7%), 9 showed a spread of the infection while under treatment (12.3%), and 16 did not report back to the clinic for complete follow-up. These patients were treated with podophyllum resin only.

TABLE 2.—*Time Required for Cure of Infections*

Cures Achieved in Microsporum (M.) Audouini Infections

Length of Time	No. of Patients
2-4 weeks	4
1-2 mo.	3
2-3 mo.	6
3-4 mo.	4
4-5 mo.	3
6-7 mo.	2
Total	22

Cures Achieved in Microsporum (M.) Lanosum Infections

Length of Time	No. of Patients
2-4 weeks	3
1-2 mo.	2
2-3 mo.	2
Total	7

Cure Achieved in Unidentified Endothrix Infection

Length of Time	No. of Patients
1-2 mo.	1

TABLE 3.—*Cures Achieved in M. Audouini Infections*

Length of Time After X-Ray Epilation	No. of Patients
2-4 weeks	5
1-2 mo.	11
2-3 mo.	3
3-4 mo.	3*
5-6 mo.	1†
6-7 mo.	1
Total	24

* One patient had x-ray epilation two years prior to the podophyllum resin treatment. Various local medications were applied unsuccessfully.
† One patient had x-ray epilation eight months prior to the podophyllum resin treatment. Various local medications were applied unsuccessfully.

On the other hand, in a series of 32 patients treated with x-ray epilation and subsequent podophyllum resin application cures were achieved in 26 (81.3%), improvement in 3 (9.4%), and no change was observed in 3 cases (9.4%). While the percentage of cures resulting from treatment that combined x-ray epilation with podophyllum resin application was larger, one should not lose sight of the additional time which was required for this combined treatment (table 3). Each patient who was epilated was treated previously for two months with podophyllum resin ointment, and epilation was instituted only in cases in which the local response was unsatisfactory. It is of added importance that in the two series the infected areas were similar in size and distribution and that the previous local therapy and subsequent x-ray epilation did not shorten the course of the disease. The fact that children epilated by x-ray had two-months' treatment preceding epilation adds two months to the total length of treatment. In both M. audouini and M. lanosum infections the shortest time for cure was between two and four weeks, and the longest was seven months. While seven-months' treatment is not unusual for infections due to M. audouini (Schwartz reported up to 10 mo.), it is rather uncommon in M. lanosum infections. However, the fact that M. lanosum hardly ever produced an inflammatory reaction in the children reported is indicative of an adaptation to the human host and a behaviour similar to M. audouini.

While we do not consider podophyllum resin the ideal solution for the treatment of tinea capitis, it is worth considering in our therapeutic armamentarium. This is particularly true in instances in which further treatment is necessary after x-ray epilation and in which small isolated areas are being treated over a considerable length of time.

SUMMARY

A report is submitted of 121 cases of tinea capitis treated with a 0.2% resin of podophyllum ointment alone and in combination with x-ray epilation. Fifty-six patients were cured, 26 with x-ray epilation combined with podophyllum resin treatment and 30 with podophyllum resin treatment alone, 19 improved, and 21 showed no change. The agent was useful in some cases of tinea capitis due to M. audouini, M. lanosum, T. crateriforme, and T. sulfureum. The length of time required to achieve clinical cure in those cases in which podophyllum resin ointment was used alone did not differ appreciably from the length of time required in those cases in which both podophyllum resin and x-ray epilation were used.

TABLE 4.—*Analysis of Results in Patients Treated with Podophyllum Resin and with Podophyllum Resin and X-Ray*

	Cured		Improved		No Change		Spread		Totals	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Podophyllum resin and x-ray	26	81.3	3	9.4	3	9.4	0	0	32	100%
Podophyllum resin alone	30	42.0	16	21.9	18	24.7	9	12.3	73	100%
Total	56	53.3	19	18.1	21	20.0	9	8.6	105	100%

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PROTHROMBIN TIME DETERMINATIONS ON PATIENTS WITH MYOCARDIAL INFARCTION

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Recent investigations of the value of anticoagulants in myocardial infarction have indicated the need for a critical analysis of the blood-clotting mechanism in this disease.[1] Observations have been reported [2] which suggest that there is an increased tendency toward a coagulation associated with coronary thrombosis. Certain studies have yielded evidence that "hyperprothrombinemia" (in reality a summation of factors producing a shortening of the prothrombin time) is one of the factors responsible for the increased clotting tendency.[3] The importance of careful inquiry into whether such a state actually exists in patients with coronary thrombosis becomes obvious when the use of the anticoagulant drugs for both treatment and prophylaxis is being considered. Opportunity to observe daily prothrombin times in patients in whom coronary occlusion with myocardial infarction developed was afforded us during studies of the use of bishydroxycoumarin (dicumarol®) in this syndrome. The data obtained from observations of a group of patients with coronary disease and myocardial infarction, who served as controls and hence did not receive anticoagulants, are presented in this report.

HISTORY

The occurrence of thromboembolic complications in myocardial infarction was emphasized in 1937 by Blumer,[4] who reported an incidence of mural thrombi in 50% of his cases. Master, Dack, and Jaffe,[5] Falk,[6] Nay and Barnes,[7] and many others, observing different series of patients with myocardial infarction due to coronary occlusion, found significantly high percentages of thromboembolic complications.

Observations made to determine whether an abnormal clotting tendency exists in the blood of patients with coronary disease or myocardial infarction have yielded conflicting data. Various methods have been employed to investigate the clotting mechanism, ranging from simple determinations of prothrombin time, based on the method of Quick, to the more complex heparin-retardation tests described by Waugh and Ruddick,[8] and the heparin tolerance test of de Takats,[2b] which seems to demonstrate an increased tendency toward coagulation.

What has been labeled as hyperprothrombinemia was observed in patients with thromboembolic disease by Shapiro [3] in 1944. Hines and Kessler [9] noted short prothrombin times in eight patients with either coronary or cerebral thrombosis. Meyers and Poindexter [10] studied prothrombin times in arteriosclerotic patients, employing the Link-Shapiro modification of Quick's method. Determinations run every three days for six weeks on 13 patients with acute coronary occlusion revealed no change in the undilute-prothrombin times, but a shortening of one to ten seconds in the dilute-prothrombin times of 10 patients occurred from 24 to 72 hours after the occlusion. Prothrombin times determined monthly in 28 patients with coronary sclerosis showed no definite trend. Similar shortening of the dilute-prothrombin time in patients with acute coronary occlusion was demonstrated by Peters, Guyther, and Brambel,[11] who found increased prothrombin activity in three of every four persons with coronary occlusion.

On the other hand, Cotlove and Vorzimer,[12] using the Link-Shapiro modification of the one-stage method of Quick to determine the prothrombin time, could find no characteristic alteration in the prothrombin time in patients with coronary occlusion or in patients with repeated attacks of angina pectoris. Similarly, Tuft and Rosenfield [13] were unable to detect an acceleration of the prothrombin-clotting time in diluted plasma in thromboembolic diseases.

METHOD

Prothrombin times were determined by the Link-Shapiro [3] modification of the Quick [14] one-stage method. The method as routinely used in our laboratory has been previously described.[15] Daily prothrombin time determinations were done when possible on whole (100%) plasma and diluted (12.5%) plasma. The prothrombin time determinations reported here are on diluted (12.5%) plasma. All tests were performed on blood samples taken in the morning and were completed within two hours after the specimens were drawn. Seventeen persons with myocardial infarction were used in this study. These patients served as controls in the study at the New York Hospital and hence did not receive anticoagulants. The criteria for the diagnosis of

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Miss M. E. Todd and Miss K. Taylor assisted in this investigation, and Miss P. Buckley did the statistical analysis under the direction of Dr. D. F. Beck.

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myocardial infarction were those set up by the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction of the American Heart Association. For comparison data, 813 control prothrombin times on 25 normal persons previously reported have been used.

OBSERVATIONS

The data on 12.5% diluted plasma prothrombin times on the 17 patients with myocardial infarction and on the 25 normal persons are shown in Table 1. The mean of the 339 determinations on the group with coronary disease was 32.29 sec., with a range of 20.7 to 50 sec. The standard deviation was 4.22. The standard error of the mean was 0.23, and the standard error of the standard deviation was 0.16. In the 813 determinations on the normal group the mean was 38.6 sec., with a range of 32 to 42 sec. The standard deviation was 2.16. The standard error of the mean was 0.08, and the standard error of the standard deviation was 0.05.

Table 2 shows the number and percentage distribution of the prothrombin times for the two groups.

TABLE 1.—*Prothrombin Times on 12.5% Plasma in Seconds**

Patients with coronary disease	No. of Determinations	Mean	Range	Standard Error of Mean	Standard Deviation	Standard Error of Standard Deviation
A. V.	16	33.08	27.6-43.0	± 0.99	3.83	± 0.70
S. P.	24	33.08	27.0-39.0	± 0.65	3.12	± 0.46
R. H. B.	23	30.97	22.9-39.0	± 0.81	3.79	± 0.57
S. S.	18	29.92	24.0-40.5	± 1.01	4.16	± 0.71
C. V.	24	30.10	24.4-39.5	± 0.81	3.88	± 0.57
M. J.	24	33.58	27.4-42.1	± 0.93	4.45	± 0.66
O. B.	25	32.07	24.4-39.6	± 0.89	4.38	± 0.63
R. P.	17	31.13	25.4-35.8	± 0.70	2.79	± 0.49
G. D.	6	34.25	30.0-40.0	± 1.72	3.85	± 1.22
A. H.	16	32.45	26.4-38.6	± 0.88	3.39	± 0.62
M. M.	18	30.16	25.0-34.9	± 0.56	2.32	± 0.40
C. A.	10	32.78	30.1-38.8	± 0.83	2.48	± 0.59
P.	16	30.44	20.7-38.3	± 1.03	3.99	± 0.73
C. F.	30	35.52	26.4-50.0	± 0.80	4.30	± 0.56
L. M.	12	34.85	26.4-43.2	± 1.59	5.28	± 1.12
S. I.	20	34.99	26.4-43.2	± 1.00	4.38	± 0.71
R. I.	40	31.23	22.6-37.0	± 0.53	3.33	± 0.37
All patients	339	32.29	20.7-50.0	± 0.23	4.22	± 0.16
25 normal persons	813	38.6	32 -42	± 0.08	2.16	± 0.05

* Computations based on ungrouped data.

When the mean of the dilute-prothrombin times for these coronary patients was compared with that for the normal persons sampled, the difference was found to be highly significant statistically (Table 1). In other words, it was found that if the true difference between these means had been zero, the probability of obtaining a mean for coronary patients 6.3 sec. or more lower than that for normal patients would be less than 1 in 1,000. In fact, the chances that the mean for coronary patients would have exceeded 33.0 sec., or that for normal patients fallen below 38.0 sec., were in each case exceedingly slight. Since the laboratory procedures were identical, except for minute random fluctuations in technic, it must be concluded that some real difference between these groups exists, the dilute prothrombin times for this sample of coronary patients being appreciably lower on the average than those of the normal persons used as controls. This test does not in any way, however, reveal the reason for the observed difference.

COMMENT

TABLE 2.—*Number and Percentage Distribution of Prothrombin Times on 12.5% Plasma in Seconds for Patients with Coronary Disease and for Normal Persons*

Prothrombin-Clotting Time, Sec.	Number of Readings		Per Cent of Total Readings	
	Patients	Normal Persons	Patients	Normal Persons
20*	1	..	0.3	...
21	..	..	...	...
22	2	..	0.6	...
23	..	..	...	...
24	6	..	1.8	...
25	7	..	2.1	...
26	12	..	3.5	...
27	17	..	5.0	...
28	22	..	6.5	...
29	26	..	7.7	...
30	47	..	13.9	...
31	29	..	8.5	...
32	31	5	9.1	0.6
33	22	18	6.5	2.2
34	26	33	7.7	4.1
35	28	45	8.3	5.5
36	17	75	5.0	9.2
37	9	120	2.6	14.8
38	11	162	3.2	19.9
39	11	146	3.2	18.0
40	6	90	1.8	11.1
41	2	69	0.6	8.5
42	1	50	0.3	6.1
43	5	..	...	...
44	..	..	...	...
45	..	..	...	...
46	..	..	...	...
47	..	..	...	...
48	..	..	...	...
49	..	..	...	...
50	1	..	0.3	...
Total readings	339	813	100.0	100.0

* Defined as 20.0 to 20.9 inclusive.

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The prothrombin times of whole (100%) plasma are not reported here, because the results are not so clear-cut as those of diluted plasma and if there is a change from normal it is very slight. The data on whole (100%) plasma prothrombin times and their significance will be reported in a subsequent communication.

In Table 2 the number and percentage distribution of the prothrombin times on diluted (12.5%) plasma for the patients with coronary disease and for normal persons are given. It should be noted that the distribution range of prothrombin times on the coronary patients is greater (20.7 to 50 sec.) than that of the normal group (32 to 42 sec.). This wide distribution range in the coronary group makes any single prothrombin time determination of limited value, but when four or five determinations are done on the same patient over a period of several days the tendency for a shortened diluted-plasma prothrombin time usually becomes apparent.

SUMMARY

The dilute (12.5%) plasma prothrombin times of a group of patients with myocardial infarction are compared with those of a group of normal persons. The group with myocardial infarction showed a mean prothrombin time of 32.29 sec. The mean of the normal group was 38.6 sec. This difference is statistically highly significant.

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EFFECTS OF ULTRAVIOLET-RAY IRRADIATION ON CLOTTING MECHANISM OF PLASMA

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Ultraviolet-ray irradiation of human plasma was introduced for sterilizing purposes after recognition of the fact that homologous serum jaundice could be transmitted in this medium. Several studies attest to its efficacy in eliminating the virus of homologous serum jaundice [1] and to its safety.[2] Recently Cutler, Burbank, and Marzullo [3] reported alterations in the clotting mechanism of irradiated plasma, attributing this to irradiation with ultraviolet rays of 1,849 A., and suggested that such plasma had anticoagulant properties.

That certain components of liquid plasma deteriorate with age has been shown in the past.[4] At the end of three months the prothrombin concentration is approximately 17% of normal, although the fibrinogen content is still intact. By the end of six months, the prothrombin level is down to 2%, and the fibrinogen has completely disappeared. The alterations in the clotting mechanism which Cutler and his associates describe are attributed to the effect of irradiation with short ultraviolet rays. We have found that the "MR plasma" used by them refers to liquid plasma collected in September, 1948, and June, 1949. The latter plasma furthermore had been diluted with an equal volume of 5% dextrose in isotonic sodium chloride solution. From the evidence cited [4] relative to the deterioration of fibrinogen, such aged and diluted liquid plasma should not be expected to clot upon the addition of thrombin, regardless of ultraviolet-ray irradiation. The "complex mechanism" proposed by Cutler and others to explain the ability of 0.3 cc. of irradiated plasma to prevent the clotting of 1.0 cc. of venous blood is thought untenable. No consideration was given by them to the presence of sodium citrate in the plasma, which would be expected to interfere with the in vitro clotting of venous blood. Because of these facts, some of the aspects of the coagulation mechanism of irradiated liquid plasma were reinvestigated.

MATERIAL AND METHODS

The human plasma used in this study was processed in accordance with the requirements of the National Institutes of Health. Ultraviolet-ray irradiation was performed according to the method of Oppenheimer and Levinson.[5] Samples of plasma of varying ages, both irradiated and unirradiated, were submitted as unknowns. Aliquot fractions, before and after irradiation, were included. Prothrombin determinations were done as prescribed by the one-stage method of Quick.[6] Thromboplastin was prepared by acetone extraction of human brain. The thrombin and heparin used were commercially available compounds [7] in concentrations of 200 units and 10 mg. per cubic centimeter, respectively. Fresh defibrinated serum was obtained by whipping with glass beads. Human serum was prepared in accordance with the method approved by the National Institutes of Health and irradiated in the same manner as the plasma. Fibrinogen was prepared according to the method of Ware, Guest, and Seegers.[8]

From the Hematology Laboratory and the Hektoen Institute for Medical Research, Cook County Hospital.

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RESULTS

Six sets of experiments were performed. The first experiment was done to determine the effect of ultraviolet-ray irradiation (utilizing 1,849 A.) on the clotting mechanism of three-month-old liquid plasma. Aliquot samples, before and after irradiation, were compared with a fresh oxalated control sample (Table 2). The results showed the clotting mechanism of both the irradiated and unirradiated samples to be inferior to that of the control sample. The unirradiated aliquot in each instance revealed a more competent clotting mechanism than its respective irradiated aliquot. This was equally true of plasma treated with ultraviolet rays of 1,849 A. and 2,537 A.

The third set of experiments compared the clotting mechanism of fresh liquid plasma with that of liquid plasma older than six months, in both the irradiated and unirradiated state (Table 3). All of the older samples, both irradiated and unirradiated, showed the same deterioration of the essential clotting elements.

To explain the failure of clot formation in the older

TABLE 1.—*Effect of Ultraviolet-Ray Irradiation on Clotting of Fresh Liquid Plasma*

	Sample A (From a Single Unirradiated 4-Day-Old Plasma Sample)	Sample B (Same as A Except Irradiated)	Sample C (Control Sample of Fresh Unirradiated 1-Day-Old Plasma)
Prothrombin time, sec.	15.0 15.2	14.4 15.0	15.0 15.0
1 unit thrombin added to 1 cc. plasma	29.0 sec. (firm clot)	35.0 sec. (firm clot)	31.0 sec. (firm clot)
1 mg. heparin and 10 units thrombin added to 1 cc. plasma	50.0 sec. fibrin strands	40.0 sec. fibrin strands	32.0 sec. (firm clot)
1 mg. heparin and 20 units thrombin added to 1 cc. plasma	35.0 sec. (firm clot)	40.0 sec. (firm clot)	.....

TABLE 2.—*Effect of Ultraviolet-Ray Irradiation on Clotting of Three-Month-Old Liquid Plasma*

	Pool of 29 Plasma Samples		Pool of 31 Plasma Samples		Pool of 32 Plasma Samples		Pool of 29 Plasma Samples		Pool of 32 Plasma Samples		Pool of 26 Plasma Samples		Pool of 30 Plasma Samples		Pool of 32 Plasma Samples		Control Samples
	Unirradiated	Irradiated	Unirradiated	Irradiated	Unirradiated	Irradiated	Unirradiated	Irradiated	Unirradiated	Irradiated	Unirradiated	Irradiated	Unirradiated	Irradiated*	Unirradiated	Irradiated	
Prothrombin time (sec.)	19.6 20.0	21.2 21.8	22.0 21.6	20.8 20.2	18.0 18.6	22.4 21.9	18.2 17.8	21.0 20.2	18.4 18.2	20.0 19.8	20.0 19.4	19.8 20.8	19.0 18.6	21.2 21.8	18.8 19.4	20.4 20.2	12.0 12.2
Clotting time (sec.) when 1 unit thrombin added to 1 cc. plasma	53.4 54.0	76.0 71.0	67.0 66.0	93.0 100.0	60.0 61.0	100.0 105.0	65.0 68.0	105.0 110.0	59.0 62.0	80.0 83.0	67.0 70.0	78.0 80.0	63.0 67.0	102.0 110.0	82.0 90.0	110.0 120.0	21.0 22.2
Clotting time (sec.) when 1 mg. heparin added to 1 cc. plasma with units thrombin added:																	
1	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	....
2	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	....
10	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	25.0
20	No clot	No clot	No clot	No clot	No clot	No clot	10.0	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	No clot	....
40	5.0	12.0	6.0	16.0	9.0	13.0	....	6.0	13.0	20.0	7.0	21.4	14.0	16.0	6.0	17.0	....

* Irradiation with 2,537 A. only.

TABLE 3.—*Effect of Age on Clotting of Liquid Plasma*

	Control Sample (Fresh Unirradiated 1-Day-Old Plasma)	Sample D (Single Sample Unirradiated 1-Day-Old Plasma)	Sample E (Pool of 8 Samples Unirradiated 2-Day-Old Plasma)	Sample F (Single Sample Unirradiated 10 Mo.-Old Plasma)	Sample G (Single Sample Unirradiated 40-Mo.-Old Plasma)	Sample H (Single Sample Unirradiated 50-Mo.-Old Plasma)	Sample I (Single Sample Irradiated 1-Day-Old Plasma)	Sample J (Pool of 34 Samples Irradiated 7-Mo.-Old Plasma)	Sample K (Pool of 33 Samples Irradiated 10-Mo.-Old Plasma)	Sample L (Single Sample Irradiated 21-Mo.-Old Plasma)	Sample M (Single Sample Irradiated 28-Mo.-Old Plasma)	Sample N (Single Sample Irradiated 34-Mo.-Old Plasma)
Prothrombin time (sec.)	13.8 13.8	15.2 15.4	14.0 14.4	No clot in 24 hr.	No clot in 24 hr.	No clot in 24 hr.	17.0 17.0	No clot in 24 hr.	No clot in 24 hr.	No clot in 24 hr.	No clot in 24 hr.	No clot in 24 hr.
Clotting time (sec.) when 1 unit thrombin added to 1 cc. plasma	21.0 21.5 (firm clot)	20.0 20.0 (firm clot)	20.0 20.8 (firm clot)	No clot in 24 hr.	No clot in 24 hr.	No clot in 24 hr.	22.0 22.4 (firm clot)	.... No clot in 24 hr.	.... No clot in 24 hr.	No clot in 24 hr.	No clot in 24 hr.	No clot in 24 hr.
20 units 40 units 200 units added	....	....	....	No clot	No clot	No clot	....	No clot	No clot	No clot	No clot	No clot
Clotting time (sec.) when 1 mg. heparin and 10 units thrombin added to 1 cc. plasma	12.2 13.0	23.0 23.2	23.0 23.6	No clot	No clot	No clot	21.0 21.0	No clot	No clot	No clot	No clot	No clot ....
Clotting time (sec.) when 1 mg. heparin and 20 units thrombin added to 1 cc. plasma	4.0 4.8	8.4 9.0	8.0 8.4	.... No clot	.... No clot	.... No clot	8.8 9.2	.... No clot	.... No clot	.... No clot	.... No clot	.... No clot

mechanism of fresh liquid plasma. Aliquot samples of plasma before and after irradiation were compared with a fresh oxalated control sample (Table 1). The results show the clotting mechanism of the irradiated plasma to be identical with the aliquot unirradiated sample and the control sample.

The second set of experiments were undertaken to determine the effect of ultraviolet-ray irradiation on the liquid plasmas, the fourth set of experiments was performed (Table 4). The addition of either 0.3 cc. of irradiated serum (fibrinogen-free) or 0.3 cc. of fresh unirradiated defibrinated serum to a mixture of 20 units of thrombin and 1 cc. of plasma failed to produce a clot. However, with the addition of 0.1 cc. of fibrinogen to this mixture, four of the samples of plasma clotted. By increasing the fibrinogen to 0.3 cc., clotting took place in

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three other samples, and with the addition of 0.5 cc. of fibrinogen the last plasma clotted. The amount of fibrinogen needed to produce clotting bore no direct relationship either to the age (these being all old plasmas) or to the exposure to irradiation. This would suggest that changes other than those already noted occur in aging plasma.

The fifth experiment was undertaken to explain the inhibition of clotting of 1 cc. of venous blood by the addition of 0.3 cc. of irradiated plasma. Because Cutler and others, is due solely to the excess citrate and does not depend upon the substrate added.

In the sixth experiment 600 cc. of irradiated liquid plasma, aged 4, 7, 9, and 10 mo., was administered to each of five recipients. Clotting times were determined 48 hr., 24 hr., and immediately prior to administration and at intervals of 1, 2, 24, 48, and 72 hr. following the start of the infusion. No prolongation of the clotting times could be demonstrated (Table 5).

TABLE 4.—*Effect Produced by Addition of Fibrinogen to Aged Liquid Plasma*

	Sample F (Single Sample Unirradiated 10-Mo.-Old Plasma)	Sample G (Single Sample Unirradiated 40-Mo.-Old Plasma)	Sample H (Single Sample Unirradiated 50-Mo.-Old Plasma)	Sample J (Pool of 34 Samples Irradiated 7-Mo.-Old Plasma)	Sample K (Pool of 33 Samples Irradiated 10-Mo.-Old Plasma)	Sample L (Single Sample Irradiated 21-Mo.-Old Plasma)	Sample M (Single Sample Irradiated 28-Mo.-Old Plasma)	Sample N (Single Sample Irradiated 34-Mo.-Old Plasma)
20 units thrombin, 1 cc. plasma, and 0.3 cc. irradiated serum	No clot in 48 hr.	No clot in 48 hr.	No clot in 48 hr.	No clot in 48 hr.	No clot in 48 hr.	No clot in 24 hr.	No clot in 48 hr.	No clot in 48 hr.
20 units thrombin, 1 cc. plasma, and 0.3 cc. defibrinated fresh serum	No clot in 48 hr.	No clot in 48 hr.	No clot in 48 hr.	No clot in 48 hr.	No clot in 48 hr.	No clot in 24 hr.	No clot in 48 hr.	No clot in 48 hr
Clotting time (sec.) with 20 units thrombin, 1 cc. plasma, 0.3 cc. irradiated serum, and 0.1 cc. fibrinogen	No clot in 48 hr.	60.0 61.0	No clot in 48 hr.	17.0	8.0	16.2 15.4	No clot in 48 hr.	No clot in 48 hr.
Clotting time (sec.) with 20 units thrombin, 1 cc. plasma, 0.3 cc. fresh defibrinated serum, and 0.1 cc. fibrinogen	No clot in 48 hr.	60.0 58.0	No clot in 48 hr.	20.0	10.0	17.4 18.6	No clot in 48 hr.	No clot in 48 hr.
Clotting time (sec.) with 20 units thrombin, 1 cc. plasma, and								
(a) 0.1 cc. fibrinogen	No clot in 48 hr.	58.0 60.4	No clot in 48 hr.	8.0	5.0	15.2 16.0	..... No clot	..... No clot
(b) 0.3 cc. fibrinogen	7	....	61	....	....	....	40	No clot 40.0
(c) 0.5 cc. fibrinogen	.....	.....	.....	....	....	....	....	45.0

TABLE 5.—*In Vivo Effect of Injection of Irradiated Aged Liquid Plasma on Clotting Mechanism*

			Preinfusion Clotting Time						A †		B ‡		Postinfusion Clotting Time					
			48 Hr.		24 Hr.		Immediate		1 Hr.		2 Hr.		24 Hr.		48 Hr.		72 Hr.	
Patient	Plasma No.	Age	Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.	Min.	Sec.
1	SP2165	9 mo.	7	10	10	20	12	..	11	..	14	30	8	30	11	30	8	30
			9	20	9	15	13	..	12	30	15	..	10	30	12	5	10	30
2	SP2146	9 mo.	8	40	10	10	12	..	12	15	11	..	11	15	Not taken		Not taken	
			11	5	12	15	12	15	14	30	14	30	11	40	..	..	..	..
3	SP2772	4 mo.	9	10	11	5	9	15	9	35	10	..	8	30	11	35	11	5
			9	5	11	15	9	30	11	5	11	30	9	5	12	50	13	30
4	SP2607	7 mo.	12	30	14	15	Not taken		10	20	12	35	10	11	9	30	Not taken	
			13	22	14	25	..	..	11	40	15	20	11	20	9	..	..	..
5	SP2078A	10 mo.	11	10	11	..	11	30	10	45	12	20	10	45	8	20	11	30
			11	40	11	15	13	..	12	..	11	45	11	10	9	..	10	5

* Clotting time determined by Lee-White method.
† Infusion started.
‡ Infusion completed.

others noted this phenomenon, they postulated "complex changes" due to ultraviolet-ray irradiation. The results of this experiment reveal that a similar quantity of unirradiated plasma also will prevent 1 cc. of venous blood from clotting. Amounts of 0.3 cc. of each of seven fresh irradiated and six fresh unirradiated samples of plasma were added individually to 1 cc. quantities of fresh whole blood obtained from 10 normal donors. No clot was noted in any of the mixtures at the end of 24 hr. Clot formation is also prevented when sodium citrate in serum or isotonic sodium chloride solution, in a concentration similar to that found in citrated plasma, is added to fresh whole blood. Quantities of 0.3 cc. of citrated isotonic sodium chloride solution and citrated irradiated serum were added to 1 cc. of fresh whole blood, and again no clot was noted at the end of 24 hr. Clot inhibition of fresh blood, therefore, as observed by Cutler and

COMMENT

Our reinvestigation of Cutler and others' work has revealed that the clotting of fresh irradiated plasma is practically the same as that of an aliquot unirradiated sample. In older plasma, in which prothrombin and fibrinogen deterioration has begun but is not yet complete, the procedure of ultraviolet-ray irradiation does alter the clotting mechanism. This alteration is of the magnitude of fractions of a minute and is produced by ultraviolet rays of both 1,849 A. and 2,537 A. Whether this effect is due to the actual irradiation or is ascribable to the mechanical trauma inherent in the procedure is as yet undetermined. The inability of aged plasma to clot is due to fibrinogen deterioration and not to irradiation with ultraviolet rays of 1,849 A., for similar changes are noted in both irradiated and unirradiated plasmas. Furthermore, these changes can be completely reversed in

both by the addition of fibrinogen. It has also been shown that the concentration of sodium citrate used in the routine collection of blood to prepare plasma is such that 0.3 cc. of plasma will prevent the clotting of 1 cc. of blood. Identical inhibition of clotting can be produced by the use of citrated isotonic sodium chloride solution or citrated serum. This phenomenon is apparently due entirely to the anticoagulant properties of sodium citrate. The administration of 600 cc. of aged irradiated liquid plasma did not affect the clotting mechanism of any of five recipients.

How can one reconcile the established clinical efficacy of stored liquid plasma with the knowledge that such plasma is incoagulable by virtue of prothrombin and fibrinogen deterioration? The answer lies in the fact that the *normal* circulating prothrombin and fibrinogen are in such excess as to be able to compensate for their absence in the infused plasma. Furthermore, significant hypoprothrombinemia is practically nonexistent, except in bishydroxycoumarin (dicumarol*) poisoning and the absence of bile from the intestinal tract. Hypofibrinogenemia or afibrinogenemia is a rare congenital disturbance, which manifests itself early in life. Too much stress has been placed on the presence of prothrombin and fibrinogen in plasma. For all practical purposes, these substances are rarely needed when plasma is used. In the occasional circumstance when fibrinogen or prothrombin is required, it is best to use fresh whole blood rather than plasma.

CONCLUSIONS

The ultraviolet-ray irradiation of fresh plasma does not alter its clotting mechanism. In plasma in which prothrombin and fibrinogen deterioration has begun, changes in the clotting mechanism are produced by ultraviolet-ray irradiation, utilizing either 1,849 A. or 2,537 A. These changes are of the magnitude of fractions of a minute. The inability of aged liquid plasma to clot upon the addition of thrombin is due to the disappearance of fibrinogen; this process can be reversed by the addition of fibrinogen. This is equally true of both irradiated and unirradiated liquid plasma. The inhibition of in vitro clotting of fresh blood by the addition of plasma is due to the sodium citrate in the plasma. The administration of aged irradiated liquid plasma in 600 cc. quantities has no effect on the clotting mechanism of recipients.

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ALTERATIONS IN THE PERMEABILITY OF MEMBRANES DURING INFECTIONS

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The underlying physiological disturbances responsible for death during the course of acute infections remain a mystery. Thousands of years ago men began to record descriptions of febrile illnesses. A particular type of rash might be accompanied by a slow or fast pulse and by a steady or remitting type of fever, which would run its course within a reasonably constant period of time and would be followed by a period of convalescence. On the basis of clinical observations, various specific diseases were separated from one another—the small from the great pox, the typhuslike, or typhoid, fever from typhus. In the course of some acute infections the appearance of edema was noted; in others edema was not visible, but diuresis occurred during recovery—an observation which suggested that fluid was retained in the tissues, whether it was obvious or not. With the introduction of immunologic techniques, it was recognized that the patient would react to the infecting agent with demonstrable immune responses, which could be used for confirmation of the diagnosis or for prognosis.

In addition to the observations on acute generalized diseases, excellent clinical descriptions of different types of local infections in wounds or the skin were recorded. Lesions characterized by a thin serous exudate, or by uniform red swelling having a sharp and rapidly spreading raised edge in the skin (erysipelas), were contrasted with those having a thick purulent exudate or with more localized swelling which remained circumscribed (a boil or carbuncle). It was recognized that the redness and heat of the inflammation were the result of a local increase in blood flow. The swelling was attributed to a loss of fluid from the blood into the tissues. The pain was ascribed to stimulation of nerve endings—the result of an increase in the tension of tissues, produced by the accumulation of fluid. If the local infection were adjacent to a serous cavity, fluid might accumulate in that space; in tuberculosis, for instance, a pleural effusion might develop early. Because of its higher protein content, the exudate produced by infection was recognized to clot more readily than fluid accumulating as the result of mechanical factors, such as heart failure or venous and lymphatic obstruction.

On the supposition that the body's reaction to generalized infectious diseases might follow the same general principles involved in its response to localized infections, we began to make observations in various specific fevers. Any alteration in the permeability of membranes occurring during the course of an infection should affect the

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fluids in the entire vascular tree, as well as their local distribution in the affected tissues. Changes in the general circulation would explain the clinical observations that a weak pulse, faint heart sounds, and cyanosis frequently precede death during infectious diseases.[1] Direct toxic myocardial damage (central circulatory failure) might then be differentiated at the bedside from peripheral collapse (peripheral circulatory failure) resulting from toxemic alterations in the permeability of membranes.

ALTERATIONS IN PERMEABILITY ASSOCIATED WITH SPECIFIC DISEASES

Alterations Occurring Within Minutes to Hours.—Meningococcemia: In meningococcemia the integrity of membranes may be altered within a matter of minutes or hours. The characteristic hemorrhagic rash is due to the rupture of capillaries by groups of organisms. A loss of capillary tone may lead rapidly to a picture of peripheral circulatory collapse, without appreciable alteration in the permeability of membranes or without visible edema. Such a sequence of events occurred in the case of a girl, 17, who was admitted to the hospital with a typical rash (Fig. 1) and with circulatory failure. The simple administration of isotonic sodium chloride solution to correct dehydration and increase the circulating blood volume was all that was required to support the circulation (Fig. 2). The acute symptoms of infection were controlled with chemotherapy.

In these mild cases of meningococcemia, slight edema may be evident after several days; in this patient subcutaneous pitting edema developed, and the plasma proteins were found to be low. Plasma was then administered to correct the hypoproteinemia. This therapeutic measure apparently increased the circulating blood volume to such an extent (once the alteration in the permeability of membranes was corrected) that an esophageal varix (the result of a pre-existing Banti's syndrome)

Fig. 1.—The hemorrhagic rash of meningococcemia on the third day of symptoms in a girl, 17. Note the edema of the fingers and back of the hand after the correction of dehydration with isotonic sodium chloride solution, which demonstrates an increase in the permeability of membranes due to toxemia. The course of the patient is shown in Figure 2.

ruptured, and hemorrhagic shock occurred. Whole blood was given to replenish that lost from the circulation. This time the increase in blood volume produced central circulatory failure, which led to a fatal pulmonary infarction.

In the hyperacute form of the disease, circulatory failure develops too rapidly for edema to become visible. Such was the case with an elderly shoemaker who entered the hospital with peripheral circulatory failure so severe that it had produced collapse of the neck and arm veins, as well as a fall in the arterial blood pressure. Because of the severity of the vascular collapse and the presence of deep cyanosis and coma, bilateral adrenal hemorrhage was suspected. Isotonic sodium chloride solution was given to correct the dehydration, but no clinical improvement resulted. Large amounts of plasma were then administered intravenously, but the blood pressure did not rise (Fig. 3). Since the failure of these

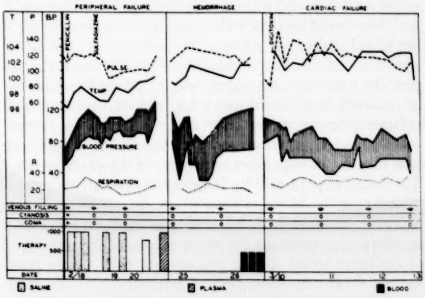

Fig. 2.—Three different types of circulatory failure occurring successively in a girl, 17, with meningococcemia with meningitis, circulatory failure, and pre-existing Banti's syndrome. Note the correction of the peripheral circulatory failure by therapy with isotonic sodium chloride solution alone and the prompt response to chemotherapy. The skin rash and edema visible in this patient on the second hospital day are shown in Figure 1. No appreciable change in the permeability of membranes occurred with the hemorrhage. Pulmonary and peripheral edema occupied the central myocardial failure. An adrenal gland removed at necropsy is shown in Figure 4.

initial therapeutic measures tended to confirm the clinical impression of adrenal failure, an aqueous solution containing 500 units of adrenal cortical hormone (50 dog units per cubic centimeter) was given intravenously. A dramatic change in the patient's clinical condition occurred after the administration of the first 150 units. The blood pressure rose, the veins filled, and the patient roused from his coma. No edema appeared, but some hours later a gallop rhythm was noted and the neck veins rapidly became distended. Acute myocardial failure developed, and the patient died.[2]

The vascular changes occurring early in the course of meningococcemia are due to toxemia from products of the infecting organism and to dehydration. The differentiation between simple toxemic peripheral circulatory collapse and that due to adrenal destruction (Waterhouse-Friderichsen syndrome) can be made clinically at the bedside and confirmed at necropsy. The adrenals in the girl showed no evidence of hemorrhage; in the man both adrenals were completely destroyed by fresh hemorrhage (Fig. 4). It is evident that the clinical differentiation between peripheral vascular collapse due to infection alone and that due to adrenal cortical destruction was correctly made in both cases. In the latter case the distribution of fluids was not appreciably altered by the adrenal cortical deficiency. The severe peripheral collapse caused the blood pressure to fall below the level

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necessary for adequate glomerular filtration. The defect in the reabsorption of sodium by the renal tubules, which leads to the excessive loss of water and salt as well as to retention of potassium, did not have time to develop, as it does in the chronic deficiency of the cortical hormone which we recognize as Addison's disease.

Alterations Occurring Within Hours or Days.—Pneumococcus Lobar Pneumonia: In pneumococcus lobar pneumonia alterations in the permeability of membranes occur over a period of hours or days. Many years ago it was discovered that chlorides were lost from the circulating blood stream but retained in tissues during the acute phase of the disease.[3] Later observations demonstrated that the extravascular space (measured by the dilution of injected thiocyanate ions) and the circulating blood volume (measured by the Evans blue technique) were increased.[4] Apparently the chloride and its companion ions take water with them as they leave the vascular tree. The defect in permeability is apparently not great enough to decrease the blood volume.

These observations offer a logical explanation of the mechanism responsible for the tendency of the right side of the heart to fail during pneumonia, particularly after the excessive administration of intravenous fluids. The usual increase in blood volume is exaggerated by the additional fluids, and the myocardium is overloaded. The favorable response to digitalis which has been noted by older clinicians is probably due to correction of the central (myocardial) circulatory failure. A direct peripheral action on the permeability of blood vessels which apparently mobilizes tissue fluids may also play a part.[5]

The additional factor of anoxia, which has long been recognized as a contributing cause for alterations in the permeability of membranes, can be illustrated more clearly in pneumococcal pneumonia than in some other infections. The presence of the pulmonary lesion decreases the size of the vascular bed available for oxygenation of the blood, and cyanosis develops.

Alterations Occurring Within Days or Weeks.—Trichinosis: In trichinosis the alteration in the permeability of membranes is pronounced and develops more gradually—over a period of days or weeks. The earliest diagnostic sign, splinter hemorrhages in the nail beds, is due to traumatic rupture of capillary loops, with extravasation of blood, as larvae migrate from the circulation into muscles (Fig. 5).[6] The accumulation of edema fluid, especially around the eyes, has been recognized as one of the most frequent early clinical manifestations of the disease. In severe trichinosis the accumulation of fluid during the stage of edema is associated with oliguria, which lasts from one to two weeks and is followed by diuresis. Serial determinations of the blood proteins made in clinically severe cases of the disease have revealed hypoproteinemia.[7] The reversible psychic disturbances occasionally seen during the stage of edema suggest an excessive hydration of nerve cells.

By the time edema is recognizable, evidence of immunity can be detected in the blood by a positive precipitin reaction or in the cells by a positive skin test. This sequence of events suggests the possibility that immunologic mechanisms may play some part in the physiological disturbances associated with the disease. This thesis has been tested by the experimental production of the disease in rabbits.[8] The physiological changes associated with alterations in the permeability of membranes were maximal just before humoral antibodies (precipitins) appeared (Fig. 6).

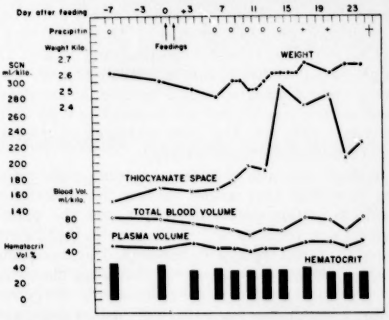

Fig. 6.—Fluid changes in a rabbit fed 6 gm. of trichinous rat meat. Note the increase in the thiocyanate space on the 14th day after the first feeding without a relative increase in body weight. The blood volume was decreased slightly during the 10th to 14th days. The physiological changes were beginning to reverse when the precipitin test became positive in the serum on the 17th day. This rabbit was severely ill, but died as the result of hematopericardium on the 25th day.

Rickettsial Spotted Fever: During the acute phase of Rocky Mountain spotted fever, the anatomic lesion is clearly reflected in the visible rash. The histological picture is essentially one of arteritis, with necrosis and thrombosis of the walls of arterioles beginning at the capillary junction. The physiological disturbance, however, may be out of all proportion to the number of pathological lesions. The permeability of the membranes gradually increases during the first two weeks of the disease, and evidences of this increase are detectable generally throughout the body, often at some distance from the arteriolar lesions.[9]

Early in the course of the disease dehydration, accompanied by a rise in the nonprotein nitrogen and a decrease in blood chlorides, may be noted.[10] The administration of solutions of crystalloids, dextrose, and isotonic sodium chloride would seem to be indicated in

3. Peabody, F. W.: Studies of the Inorganic Metabolism in Pneumonia with Especial Reference to Calcium and Magnesium, J. Exper. Med. **17**: 71-82 (Jan.) 1913. Wilder, T. S., and Drake, T. G. H.: Metabolism of Chloride and Total Fixed Base in Pneumonia and the Relation to Salt and Water Retention, J. Clin. Invest. **7**: 353-364 (Aug.) 1929.

4. Rutstein, D. D.; Thomson, K. J.; Tolmach, D. M.; Walker, W. H., and Floody, R. J.: Plasma Volume and "Extravascular Thiocyanate Space" in Pneumococcus Pneumonia, J. Clin. Invest. **24**: 11-20 (Jan.) 1945.

5. Aikawa, J. K.; Knight, V. H., and Tyor, M. P.: Effect of Intravenous Digitoxin on Fluid Distribution in Hospitalized Males without Cardiovascular Disease, Proc. Soc. Exper. Biol. & Med. **76**: 250-252 (Feb.) 1951.

6. McNaught, J. B.: The Diagnosis of Trichinosis, Am. J. Trop. Med. **19**: 181-192 (March) 1939.

7. Hanes, F. M.: Trichinosis Complicated by Hypoproteinemia, Internat. Clin. **4**: 67-73 (Dec.) 1936.

8. Aikawa, J. K.; Harrell, G. T., and Miller, T. B.: The Immunophysiology of Trichinosis: Alterations in the Blood Volume and the Thiocyanate Space in Relation to the Development of Humoral Antibodies in the Rabbit, J. Clin. Invest. **30**: 575-581 (June) 1951.

9. Harrell, G. T., Jr.: Rocky Mountain Spotted Fever, Medicine **28**: 333-370 (Dec.) 1949.

10. Harrell, G. T.; Venning, W., and Wolff, W. A.: The Treatment of Rocky Mountain Spotted Fever, with Particular Reference to Intravenous Fluids: A New Approach to Basic Supportive Therapy, J. A. M. A. **126**: 929-934 (Dec. 9) 1944.

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such a situation. When crystalloids are given, however, the blood pressure may fall to shock levels and edema which has been minimal may become more pronounced (Fig. 7). At the time that circulatory failure or edema is detected, the level of the blood proteins are found to

Fig. 7.—Marked edema in a girl, 4 yr., severely ill with Rocky Mountain spotted fever. The photograph on the left was made on the 16th day of rash. The photograph on the right, taken three weeks later during convalescence, illustrates the subsidence of edema with recovery. The clinical course of the patient is summarized in Figure 8.

be low; the administration of preformed human protein in the form of albumin, plasma, or whole blood is then indicated.

Studies on the mechanism responsible for the circulatory changes have shown that the thiocyanate space is increased and the blood volume decreased during this critical period (Fig. 8).[11] When the intravascular osmotic pressure is maintained with plasma or blood, fluid is retained in the circulation, the blood pressure is increased, and the kidneys' powers of filtration are improved. Edema is decreased, and the effects of the physiological disturbances resulting from changes in permeability are lessened. If fluids are properly selected, large amounts may safely be given parenterally. We have,

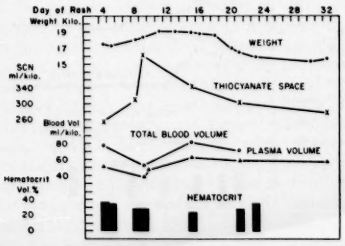

Fig. 8.—Alterations in the fluid spaces in a girl, 4 yr., severely ill with Rocky Mountain spotted fever, which was treated with supportive therapy alone. Note the rise in thiocyanate space with a drop in the blood volume on the 10th day of rash. These changes were accompanied by peripheral circulatory collapse, which was successfully treated by intravenous administration of human serum albumin. The photograph of this patient, on the left of Figure 7, was taken after the clinical peak of the disease as the symptoms were beginning to subside.

for instance, previously reported the case of a small child whose entire circulating blood volume was twice completely replaced, first with an equivalent amount of proteins and then with an even larger amount of crystalloids.[12]

The early administration of effective chemotherapeutic agents which directly attack the rickettsiae will rapidly change the character of the rash (Fig. 9) and prevent the development of further edema (Fig. 10).[13]

Alterations Occurring in Immune Reactions.—Serum Sickness: When humoral antibodies produced by an immunized animal are used to assist the patient in overcoming his infection, another illness, serum sickness, often results. In many of its clinical aspects, such as fever, malaise, and skin eruption, serum sickness resembles an infectious disease. Indeed, edema, wheals in the skin, and swelling of the joints have long been recognized as prominent features of this illness; all these suggest that immune reactions can produce alterations in the permeability of membranes. In serum sickness resulting from the administration of Rocky Mountain spotted fever antiserum prepared in rabbits, measurements of the extravascular space (by the thiocyanate technique) show the same alterations which are seen in the original infection (Fig. 11). Similar changes have been observed in patients who have received diphtheria antitoxin prepared

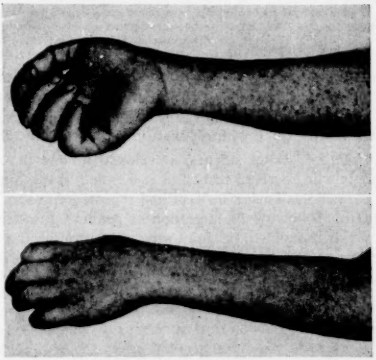

Fig. 9.—The rash in a severe case of rickettsial spotted fever in a girl, 8 yr., treated with specific chemotherapy. The photograph at the top shows the hemorrhagic character of the eruption with edema of the hand and fingers at the time of admission on the ninth day of rash. The photograph at the bottom shows the marked fading of the rash with subsidence of edema and wrinkling of the skin on the hand four days later after treatment with aureomycin. The alterations in the fluid spaces are shown in Figure 10.

in horses (Fig. 12). After the administration of antireticular cytotoxic serum (ACS) prepared in rabbits, alterations in permeability have been demonstrated in the absence of any infection. An increase in the thiocyanate space and a decrease in the blood volume have been found to occur in serum sickness experimentally

11. Harrell, G. T., and Aikawa, J. K.: Pathogenesis of Circulatory Failure in Rocky Mountain Spotted Fever: Alterations in the Blood Volume and the Thiocyanate Space at Various Stages of the Disease, Arch. Int. Med. **83**: 331-347 (March) 1949.

12. Harrell, G. T.; Aikawa, J. K., and Kelsey, W. M.: Rocky Mountain Spotted Fever, Am. Pract. **1**: 425-435 (April) 1947.

13. Harrell, G. T.; Meads, M., and Stevens, K.: "Aureomycin" A New Orally Effective Antibiotic: Clinical Trial in Rocky Mountain Spotted Fever, Results of Susceptibility Tests and Blood Assays Using a Turbidimetric Method, South. M. J. **42**: 4-13 (Jan.) 1949.

produced in rabbits by the injection of fractions of human plasma.[14]

The clinical picture of serum sickness may follow the injection of antibiotics, such as penicillin (Fig. 13). When this reaction occurs, circulating antibodies to

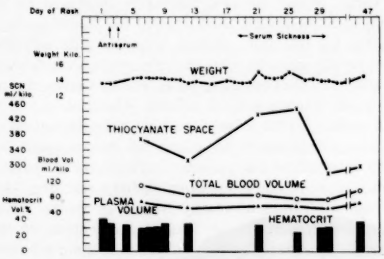

Fig. 11.—Alterations in the fluid spaces in a girl, 3 yr., with moderately severe rickettsial spotted fever treated with specific rabbit antiserum. Note the decrease in thiocyanate space on the 11th day as the clinical symptoms began to subside. The development of serum sickness on the 18th day after injection of Rocky Mountain spotted fever antiserum reproduced symptoms of infection, with fever and edema accompanied by a second rise in the thiocyanate space. The symptoms of serum sickness were controlled by the oral administration of diphenhydramine (benadryl®) hydrochloride with return of the thiocyanate space to baseline values.

penicillin (precipitins) are usually detectable. In other instances the immune (or sensitivity) reaction appears to take place predominantly on cells and is manifested by dermatitis, often with exfoliation.

Prolonged serum sickness developed in one of our patients who received penicillin suspended in oil. Since the patient was known to have had repeated episodes of stomatitis following the ingestion of peanuts, the sensitivity was thought to be due to the peanut oil used as a menstruum and not to the penicillin. Apparently the injection of any material which is allergenic to a particular patient may produce alterations in the permeability of membranes (Fig. 14).

COMMENT

Alterations in Capillary Permeability.—The observations reported can be interpreted as indicating an increase in the permeability of the vascular tree, permitting the progressive loss of crystalloids, colloids, and red blood cells from the circulation as the magnitude of the capillary defect increased with the clinical severity of the disease. The alterations in the vascular tree can be visualized as a series of pores or openings in the capillary wall where the normal extravascular circulation of crystalloids and, to a lesser extent, of small protein molecules is known to occur. In mild cases, water and ions which normally traverse the membranes would leave the blood more readily. Larger molecules, such as albumin and other proteins, would be lost in severer instances, while red blood cells would pass out of the vascular tree only in the extremest reactions.

14. Aikawa, J. K., and Harrell, G. T.: The Immunophysiology of Serum Sickness: Alterations in the Blood Volume and Thiocyanate Space in Relation to the Development of Humoral Antibodies in the Rabbit, J. Clin. Invest. 30: 360-368 (April) 1951.

15. Aikawa, J. K.: The Significance of the Radiosodium Space in Human Disease: A Comparison with the Thiocyanate Space, South. M. J. 44: 654-661 (July) 1951.

Alterations in Permeability of Cellular Membranes.—The permeability of cell membranes is probably altered too, though no techniques are available for direct measurement of cellular changes. Viruses and rickettsiae are obligate intracellular parasites. Many bacterial infections—particularly those with a chronic or prolonged course, such as tuberculosis and brucellosis — pass through a phase in which the organisms are found intracellularly. During this stage the diffusion of toxemic products of the organism must be through the cell wall, with the attendant danger of damage. Furthermore, any immune reaction would take place within the cell, so that substances released in the process would affect primarily the parasitized cells. Additional light on the problem of cellular permeability may be shed by experiments now in progress,[15] utilizing the radioactive isotopic dilution technique with Na^{24} and K^{42}.

In children acute infections accompanied by diarrhea are reported to produce a potassium deficiency. How much of this deficiency is due to a change in the permeability of cellular membranes as a result of the infection itself and how much is due to the disturbances in fluid balance associated with the diarrhea is unknown. In either event potassium moves out of the cell in which the membrane of the cell wall normally retains it and is lost in the urine or feces.

An analogous situation in which the permeability of cellular membranes is altered in the absence of infection is illustrated by the edema occurring in a young woman with drug intoxication which followed the therapeutic administration of an arsenical preparation (Fig. 15). Arsenic apparently poisons intracellular enzyme systems which contain sulfhydryl (SH) groups in the molecule. The administration of British anti-lewisite (BAL), a substance which has large numbers of accessible sulf-

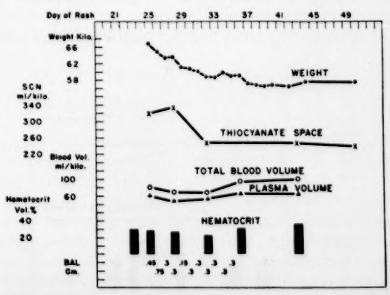

Fig. 15.—Fluid changes during arsenic intoxication (treated by inactivation) in a pregnant woman, 39, with early syphilis treated by intravenous injections of oxophenarsine hydrochloride (mapharsen®). The dermatitis appeared after the seventh injection, and the patient rapidly became ill. Note the decrease in thiocyanate space and weight following the administration of BAL. Clinical photographs of the patient are shown in Figure 16.

hydryl groups, will rapidly correct the enzymatic defect by combining with the metal. With correction of the defect, the alteration in the permeability of membranes is reversed and edema disappears (Fig. 16). Observations of this type may give further clues to the mechanism responsible for production of cell defects. Such

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questions are of more than academic interest, and are important in the design of therapy for acute infections. Intracellular enzyme systems are greatly affected by the hydration of cells and by the intracellular concentrations of ions from salts.

Fig. 16.—Edema and exfoliative dermatitis due to arsenic intoxication in a pregnant woman, 39. The photograph on the left was taken on the 27th day of rash, two days after the institution of therapy with British anti-lewisite. Note the generalized character of the edema and the scaling of dead skin. The photograph on the right was taken three months later showing complete subsidence of signs. The patient presented essentially the same appearance two weeks after the institution of therapy, illustrating how rapidly changes in permeability may revert with repair of the cellular defect.

Therapeutic Possibilities. — When infections produce an alteration in the permeability of membranes, treatment with maximum therapeutic doses of effective chemotherapeutic agents should be begun promptly in order to reduce the number of organisms and to prevent further damage. In diseases which frequently produce severe alterations in permeability—the rickettsial diseases, for example—every attempt should be made to prevent, in so far as possible, the development of the full-blown clinical picture seen in the natural course of the disease.

Salt, dextrose, and water must be administered with care. The drop in circulating proteins may be prevented or limited by the administration of a high-protein diet from the beginning of therapy.[16] When the patient is seen late in the course of the disease, after the proteins in the blood and tissues have been depleted, or after acute circulatory collapse has developed, preformed proteins in the form of concentrated human serum albumin, plasma, or whole blood must be administered. Fluid replacement therapy in specific diseases and under specific circumstances is discussed further in the illustrative cases presented in the section entitled "Alterations in Permeability Associated with Specific Diseases."

The fact that, in patients with serum sickness, administration of antihistaminic drugs relieves the joint pain and swelling and causes the wheals to disappear suggests that these drugs may find a useful place in the treatment of acute infections which have a large element of hypersensitivity. Salicylates and the closely related chemical compounds para-aminobenzoic acid (PABA) and procaine have long been successfully employed in the treatment of disease associated with immune reactions.

Metabolic factors which affect the permeability of membranes during the course of infections are as yet poorly understood. It is not known whether the increase in metabolic rate observed during infections is an attempt by the body to compensate for the defect in permeability by increasing thyroid function. It is well recognized, however, that when the thyroid function is lowered, as in myxedema, the membranes become more permeable and fluid is retained in the tissues.[15] The salicylates apparently help to correct the defect in permeability in serum sickness; they may, through their antipyretic effect, also depress the increased level of metabolic activity.

Many ingenious theories have been proposed concerning the role of the adrenal in acute infections or in diseases which are indirectly related to the stress of illness.[17] In instances of adrenal destruction (Waterhouse-Friderichsen syndrome) occurring during meningococcemia, the indications for hormone-replacement therapy are clear. The decision to use adrenal cortical hormones must be made on clinical grounds. The necessary observations on the pulse, respirations, blood pressure, venous filling, and the degree of cyanosis and edema can be made at the bedside with the equipment usually carried in a physician's bag.

Corticotrophic hormone (ACTH) or cortisone often will dramatically relieve the symptoms of serum sickness and quickly restore the physiological integrity of the membranes (Fig. 14). In patients with pneumonia a reduction in the degree of toxemia and an increase in the sense of well-being following the administration of these hormones have been reported.[18] The possible usefulness of these hormones in the treatment of diseases which characteristically are associated with high degrees of allergy, such as tuberculosis, is still under investigation. It should be emphasized that the infecting agent is not attacked by the hormones and that they have no effect on bacteremia, if this is present; their action is solely on the tissues of the host. The suppression of toxemic reactions in the host may actually be accompanied by an increase in the number of organisms and an exacerbation of the disease.[19] This sequence of events has long been recognized by clinicians in the recrudescence of clinical tuberculosis following the termination of pregnancy.

The sudden release of large amounts of antigen by the rapid destruction of organisms (such as the Herxheimer reaction which occurs in syphilis after the initial injection of penicillin) or by the dissolution of a granuloma (as occurs in some fungus infections after the administration of iodides) may not prove so detrimental to the patient if the harmful effects of the antigens on sensitized cells can be ameliorated by hormone therapy. Conversely, the apparent stimulating effect which hormone therapy has on the growth of the etiological agent may possibly be

16. Harrell, G. T.; Wolff, W. A.; Venning, W. L., and Reinhart, J. B.: The Prevention and Control of Disturbances of Protein Metabolism in Rocky Mountain Spotted Fever: The Value of Forced Feedings of a High-Protein Diet and of the Administration of Specific Antiserum, South. M. J. **39**: 551-558 (July) 1946.

17. Selye, Hans: The Physiology and Pathology of Exposure to Stress, Montreal, Acta, Inc., 1950.

18. Kass, E. H.; Ingbar, S. H., and Finland, M.: Effects of Adrenocorticotropic Hormone in Pneumonia: Clinical, Bacteriological and Serological Studies, Ann. Int. Med. **33**: 1081-1098 (Nov.) 1950.

19. Lurie, M. B.; Zappasodi, P.; Dannenberg, A. B., Jr., and Swartz, I. B.: Constitutional Factors in Resistance to Infection: The Effect of Cortisone on the Pathogenesis of Tuberculosis, Science **113**: 234-237 (March 2) 1951. ACTH and Cortisone in Active Infections, editorial, Arch. Int. Med. **87**: 1-3 (Jan.) 1951. Cortisone in Tuberculosis, editorial, J. A. M. A. **145**: 907 (March 24) 1951.

counteracted by the simultaneous or prior administration of specific chemotherapeutic agents.

In the final analysis, however, the patient must still heal himself. In spite of the most vigorous and carefully planned therapy, failures will occur. Patients will die of the toxemia of overwhelming infections and as the result of extensive vascular or cellular damage. However, intelligent management, with attention to alterations in the permeability of membranes, will allow the salvage of many cases now considered hopeless, will lessen the severity of the patient's reaction to his infection, and will shorten convalescence.

CONCLUSIONS

Our observations indicate that the permeability of membranes is altered during the course of acute infections. Early in the course of the disease the defect is probably induced by the toxemic products of the infecting organisms. Later in the course of the illness the defect may result from an immune reaction. In rickettsial diseases, for instance, the greatest alteration in permeability appears to come at the time when immunity is rising most rapidly; the balance between the antigens liberated from or secreted by the organisms and the antibody produced by the host is being rapidly destroyed.[11] The point at which immunity overcomes the infection and the antibodies begin to appear in excess often is accompanied by a dramatic clinical change which is recognized as a crisis.

Antigen-antibody reactions are known to liberate a histamine-like substance. That histamine alters the permeability of membranes locally can be readily demonstrated by the intracutaneous injection of a small amount of the material; within a few minutes a wheal appears at the site of injection (Fig. 17). Petechial hemorrhages have been recognized for years as a manifestation of anaphylactic reactions, a further clue to the mechanism of production of lesions in infections.

Since certain fundamental principles are common to all infectious diseases, alterations in the permeability of membranes can be detected in many infections occurring naturally in human beings or produced experimentally in animals. The observations reported indicate that the reactions are qualitatively similar, whether produced by a bacterial infection (meningococcemia), and extracellular infection due to a nematode (trichinosis), an intracellular infection caused by rickettsiae (Rocky Mountain spotted fever), or even an immune reaction occurring in the absence of actual infection (serum sickness).

SUMMARY

The permeability of membranes is altered during the course of acute infections. Edema develops during the acute phase, associated with an increase in extravascular fluid (thiocyanate space), and disappears with recovery. The alterations may occur within minutes to hours (meningococcemia), within hours to days (pneumococcus pneumonia), or within days to weeks (trichinosis and rickettsial spotted fever). The alterations in permeability which occur during immune reactions in the absence of infection (serum sickness) resemble the changes seen during an acute infectious disease. The observations are interpreted as indicating an alteration in the permeability of the capillary wall, permitting the progressive loss of crytalloids (water, ions, and dextrose), colloids (albumin and other proteins), and red blood cells as the clinical severity of the disease increases. These changes are often associated with alterations in blood volume and offer an explanation of the mechanism by which peripheral circulatory failure develops. The permeability of cell membranes is probably also altered, whether the cells are directly parasitized or not. The alterations during arsenic intoxication, which are reversible by therapy with British anti-lewisite (BAL), offer a clue as to a possible intracellular mechanism through interference with enzyme groups. The therapeutic possibilities are discussed, with emphasis on the correct use of crystalloids and proteins and the possible application of antihistamines and hormones in conjunction with specific chemotherapeutic agents in treatment. The early changes are due to toxemic products of the infecting organism; the later changes may result from humoral or cellular immune reactions. The alterations in permeability are qualitatively similar, whether produced by a bacterial infection (meningococcemia), an extracellular infection due to a nematode (trichinosis), an intracellular infection caused by rickettsiae (Rocky Mountain spotted fever), or an immune reaction in the absence of infection (serum sickness).

Bowman Gray School of Medicine.

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CLINICAL NOTES

TUBERCULOSIS FOLLOWING CORTISONE THERAPY

REPORT OF A CASE OF RAPIDLY PROGRESSIVE PULMONARY TUBERCULOSIS FOLLOWING CORTISONE THERAPY FOR RHEUMATOID ARTHRITIS

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John B. Johnson, M.D.,
Gilbert S. Batten, M.D.
and
Walter Lester Henry, M.D., Washington, D. C.

Experts in the field of tuberculosis have expressed concern that in some cases prolonged use of cortisone or corticotrophin (ACTH) may cause a lowering of a patient's resistance against tuberculosis. As a result the National Tuberculosis Association recently published the following recommendation:[1]

Because the action of ACTH and cortisone upon factors of resistance to tuberculosis has been shown to be deleterious in at least three species of experimental animals (mice, guinea pigs, and rabbits), and there is strongly suggestive evidence along the same lines in human beings, it is recommended that these substances not be used in patients with active tuberculosis, and that

From the Federal Security Agency, Food and Drug Administration (Dr. King) and the Department of Medicine, Howard University, and Freedmen's Hospital (Drs. Johnson, Batten, and Henry).

1. Bull. Nat. Tuberc. A. 37:4 (Jan.) 1951.

they be used with extreme caution even in human beings with possibly latent tuberculosis infection, until such time as further investigative work has shown that such administration may be safe. The routine diagnostic examination for tuberculosis of patients under physicians' care is especially necessary for patients who are being considered for ACTH or cortisone therapy.

Among the animal studies referred to in the above statement are those by Spain and Molomut [2] and Cummings.[3] Freeman [4] reported a spread in one of two tuberculous patients under treatment with ACTH. Bogan [5] and others have observed similar effects following cortisone therapy, but were not positive whether the effects owing to the drug or to the disease process itself.

In view of these observations, we are presenting the following case which, based on clinical and roentgenologic findings, has been interpreted as the development of rapidly progressive pulmonary tuberculosis following cortisone therapy in a patient with rheumatoid arthritis, in whom there was no roentgenologic evidence of active or latent pulmonary tuberculosis when cortisone therapy was initiated, or during a period of 17 years prior to treatment.

REPORT OF A CASE

R. A., a woman aged 39, single, had been under medical observation for a period of over 17 years. During her early twenties she had been frail and had shown easy fatigability. Although not considered in good health, she was able to complete her education and follow her occupation. Numerous x-ray studies of her chest made during the past 17 years did not reveal any lesions which were interpreted as active or latent tuberculosis.

In 1947, the patient first began to have joint manifestations starting in the ankles, consisting of pain, stiffness, and swelling. Later, the knees, wrists, and the joints of the hands became similarly involved. In 1948, she was hospitalized because of pneumonitis, complicated with anemia, fever, and joint involvement. Because of a failure to respond to penicillin, she received streptomycin for a short time. A rash soon developed over the face, which was followed immediately by a generalized skin eruption over the body. This episode was considered to represent a sensitivity reaction. The rash disappeared soon after streptomycin was discontinued. During this first hospitalization, laboratory data revealed evidence of a microcytic anemia and impairment of liver function as determined by the cephalin-cholesterol liver function test. Several roentgenologic examinations of the chest were made during this period. These showed transient enlargement of the cardiac silhouette suggesting pericardial effusion. After several months' hospitalization, the patient was discharged, improved.

About one year later, January, 1950, the patient was again hospitalized complaining of weakness, periodic numbness and tingling of the fingers, and pain, swelling, and stiffness of the joints of the wrists, hands, shoulders, knees, and ankles. A diagnosis of disseminated lupus erythematosus was entertained, but biopsy of the skin and muscle failed to confirm this impression. The arthritis was regarded as the rheumatoid type. The patient was discharged after two months' hospitalization, slightly improved.

By May, 1950, the rheumatoid arthritis had become so severe as to incapacitate the patient completely. The joint pain and stiffness were of such severity that she could not turn over in bed or get out of bed unassisted. There was no x-ray evidence of ankylosis. At this time, she was hospitalized for cortisone therapy.

On May 11, 1950, the laboratory findings included a red blood cell count of 3,990,000 per cubic millimeter; a hemoglobin value of 76%; a hematocrit value of 34%; an erythrocyte sedimentation rate of 65%; a white blood cell count of 10,400, with a differential count of neutrophils, 65%; lymphocytes, 34%; basophils, 1%; with 1% reticulocytosis. The urinalysis findings at that time were entirely normal. On May 10, 1950, nonprotein nitrogen was 22 mg. per 100 cc.; total protein, 6.96 gm. per 100 cc. with 2.35 gm. albumin and 4.61 gm. globulin. The x-ray of the chest three months prior to the institution of cortisone therapy revealed that there was no significant tuberculous lesion (Fig. 1).

The patient was started on cortisone on May 12, 1950, and a total of 800 mg. of cortisone was given by intramuscular injection during the first four days. (Table contains complete dosage schedule.) Within three hours after cortisone was started, the patient showed marked clinical improvement. She had less pain and could move about in bed freely. Within 48 hours the patient was able to arise from bed unassisted and was able literally to run slowly in the hospital corridors. The patient was discharged from the hospital on May 17, 1950, much improved. Cortisone treatment was continued on an outpatient basis with the objective of finding the minimum dosage which would give the maximum relief of symptoms.

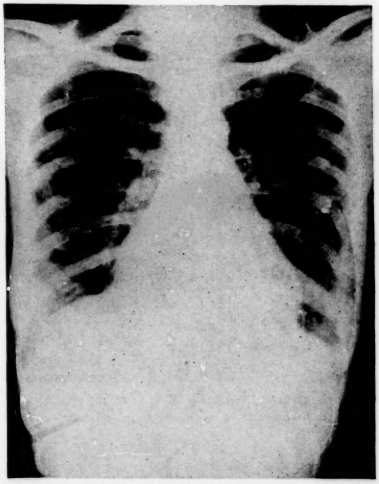

Fig. 1.—X-ray of chest of patient R. A. three months prior to institution of cortisone therapy, revealing no significant tuberculous lesion.

Complete Dosage Schedule of Patient R. A.

Month	Cortisone (Mg.)
1st (May 11 to June 9)	
1st week	900
2nd week	350
3rd week	400
4th week	300
2nd (June 10 to July 10)	1,200
3rd (July 10 to Aug. 11)	1,200
4th (Aug. 12 to Sept. 5)	900
5th and 6th (Sept. 6 to Nov. 10)	0
7th (Nov. 11 to Dec. 1)	1,400

At the time of discharge from the hospital, the patient had experienced no change in blood pressure, change in heart size, rounding of the face, or any other adverse signs of therapy.

2. Spain, D. M., and Molomut, N.: Effects of Cortisone on Development of Tuberculous Lesions in Guinea Pigs and on Their Modification by Streptomycin Therapy, Am. Rev. Tuberc. **62**: 337 (Oct.) 1950.

3. Cummings, M. M.: Influence of Cortisone on Experimental Tuberculosis, in Transactions of the 10th Veterans Administration Conference on Chemotherapy of Tuberculosis, Jan. 25, 1951, to be published.

4. Freeman, S.; Fershing, J.; Wang, C. C., and Smith, L. C.: Effect of ACTH on Patients with Pulmonary Tuberculosis, in Mote, J. R.: Clinical ACTH Conference, Proceedings of First Conference, Philadelphia, The Blakiston Company, 1950, p. 509.

5. Bogan, Emil: Adrenocortrophic and Adrenocorticogenic Hormones in Tuberculosis, in Transactions of the 10th Veterans Administration Conference on Chemotherapy of Tuberculosis, Jan. 25, 1951, to be published.

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In August, 1950, during therapy with cortisone, she experienced an episode of pain in the right hip, diagnosed as probable bursitis. This pain did not yield to cortisone therapy, but required adjunct therapy with procaine injections and x-ray therapy.

After mid-September, 1950, the patient felt so well that cortisone and other therapy was discontinued. She was sufficiently improved so that she was able to return to her usual occupation.

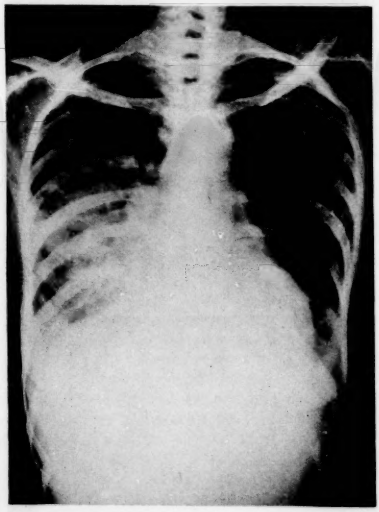

Fig. 2.—X-ray of chest of patient R. A., taken Nov. 27, 1950, showing a lesion that is characteristic of aspiration pneumonitis and, in all probability, tuberculosis.

During the second week in November the arthritic pains recurred with such severity as to require cortisone therapy to be resumed. At this time she was placed on oral cortisone, 25 mg. daily. On Nov. 20, 1950, the dose was increased to 100 mg. daily for nine days. This dosage was maintained until Dec. 1, 1950, after which no further cortisone was given. At this time hospitalization was advised because of facial edema, hyperpnea, tachycardia, and x-ray evidence of pneumonitis at the right lung base. However, the patient refused hospitalization.

The roentgenologic findings on Nov. 27, 1950, revealed that there was in the right lung a largely hemogenous dense infiltration below the fifth posterior rib. There were, however, numerous rounded rarefactions approximating 8 cm. in diameter. In the left lung there was a scanty infiltration composed of faint spots. The comment of the expert in the field of tuberculosis who interpreted the film was that the lesion is characteristic of aspiration pneumonitis and, in all probability, tuberculous. The extension of the apical infiltration showing faintly in the left on the original films contributes to this impression (Fig. 2).

On Jan. 4, 1951, the patient entered the hospital critically ill. She was febrile and extremely dyspneic, and her joints were exquisitely painful. She had a weak, nonproductive cough. The x-ray at this time was interpreted by experts in the fields of roentgenology and tuberculosis (Fig. 3). The right lung was completely occupied with infiltrations of greater density than in the film of November, with numerous punched out factions. The left lung revealed extension of the infiltration with a rarefaction of 1 cm. in the circle of the first rib. Scanty infiltration was scattered through the rest of the lung. From a roentgenologic standpoint this case was considered as being acute caseous tuberculosis of the type seen in the aged, terminal uremics, diabetics, or in the very young. Based on the combined roentgenologic and clinical findings, the diagnosis was that of a fulminating tuberculous pneumonia. The patient's course was rapidly downhill, and she died on Jan. 8, 1951. Request for autopsy was denied.

6. Kass, E. H.; Ingbar, S. H., and Finland, M.: Effects of Adrenocorticotropic Hormone in Pneumonia: Clinical, Bacteriological and Serological Studies, Ann. Int. Med. 33: 1081 (Nov.) 1950. Hench, P.: Effects of Cortisone in Rheumatic Diseases, Lancet 2: 483 (Oct. 21) 1950.

COMMENT

It is realized that a confirmed diagnosis of tuberculosis was not made in this patient, since tubercle bacilli were not found while the patient was living, nor was an autopsy performed. However, based on careful clinical and roentgenologic findings, the diagnosis was that this patient died from a rapidly progressive tuberculosis. The case is reported primarily to emphasize that extreme care should be taken in ruling out active or latent tuberculosis prior to the institution of prolonged cortisone or ACTH therapy until further studies are made to determine whether these drugs may or may not have an adverse effect in the spread of the disease.

In this case, the cortisone apparently had a deleterious effect on old, seemingly insignificant, tuberculous focuses in the patient's lung fields. It has been reported [6] that in many infectious diseases the organisms continue to grow despite the administration of cortisone, though the patient feels better and in many cases eventually overcomes his infection. When cortisone is given to tuberculous animals, a remarkable lack of limitation of spread of tuberculous processes is seen. Fibroplasia is inhibited and freedom of movement through the tissues by the tubercle bacilli is facilitated.

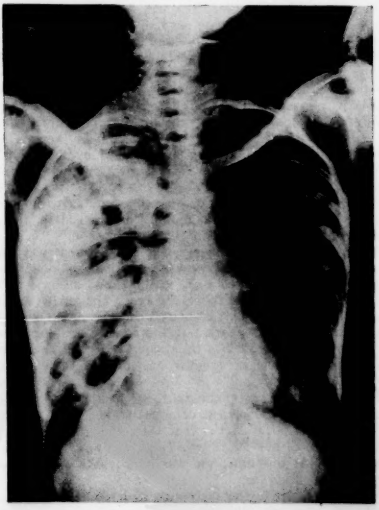

Fig. 3.—X-ray of chest of patient R. A. taken Jan. 4, 1951, showing spread, with x-ray diagnosis of acute caseous tuberculosis.

Presumably there was a spread of tubercle bacilli throughout this patient's lungs that was initiated by cortisone therapy. Her generalized debilitated condition was a further factor in its rapid spread. Interference with

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macrophage activity and depletion of lymphoid tissue by prolonged cortisone administration were most likely additional contributory deleterious factors.

X-ray studies have been conducted on a large group of patients who have received cortisone over prolonged periods. In these patients, no instances of pulmonary complications have been encountered.

It is recommended that all patients who are to undergo prolonged therapy with cortisone be carefully studied prior to and during treatment to determine whether a latent or active tuberculosis exists or develops.

U. S. Food and Drug Administration, Federal Security Agency, Washington 25, D. C. (Dr. King).

CORTISONE AND PULMONARY TUBERCULOSIS

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Poul Ottosen, M.D.
and
Charles A. Brasher, M.D., Mount Vernon, Mo.

A warning against the use of corticotrophin (ACTH) and cortisone not only in patients with active tuberculosis but also in patients with latent tuberculous infection was issued a few months ago by the Committee on Medical Research of the American Trudeau Society, in the Bulletin of the National Tuberculosis Association.[1] In a subsequent issue of the Bulletin, Tucker [2] again emphasized the danger of the use of ACTH and cortisone in the tuberculous patient.

Spain and Molomut [3] described the effect of cortisone in guinea pigs experimentally infected with tuberculosis. The lesions in those animals receiving cortisone appeared to be more extensive and less well localized than in control animals that did not receive cortisone.

In an editorial in THE JOURNAL, March 24, 1951,[4] the suggestion is issued that caution should be exercised in the administration of cortisone to patients with tuberculosis. This suggestion is made as a result of tests on tuberculous animals.

To our knowledge, no report has been made, until the present time, about the ill effect cortisone may have on human beings who are infected with pulmonary tuberculosis. We therefore feel that the following case report may be of interest to the medical profession.

REPORT OF A CASE

A. G., a white woman aged 64, was admitted for the second time to the Missouri State Sanatorium on June 21, 1950, because of far-advanced bilateral tuberculosis, with doubtful activity.

The patient was first admitted to the Missouri State Sanatorium March 1, 1947, with a far-advanced case of active pulmonary tuberculosis. Figure 1 shows the first x-ray taken at the time of her first admission.

She gave a history of gradual onset of her disease with cough, chest pain, low grade temperature, and gradual loss of weight of about two years' duration.

In April, 1935, she was a patient at the Mayo Clinic, Rochester, Minn., and a diagnosis of rheumatoid arthritis and bronchial asthma was made. X-rays of the chest were negative at that time.

During her first admission she had 21 sputum examinations for tubercle bacilli. All were negative on direct smear. Guinea pig inoculation and culture were both negative for acid-fast organisms. Tuberculin skin tests were positive on old tuberculin, dilution 0.005. Other tests made gave no further information. A diagnosis of pulmonary tuberculosis was made at that time entirely from chest x-rays, evidence of positive skin test, and from clinical history.

Fig. 1.—First x-ray of patient A. G., taken at the time of her first admission to the Missouri State Sanatorium, March 1, 1947.

On her first admission to the Missouri State Sanatorium she also showed evidence of marked rheumatoid arthritis and secondary anemia.

During this first admission the patient had no other treatment than bed rest and symptomatic treatment for arthritis. She was discharged Nov. 28, 1948. At discharge the patient's tuberculosis was considered as arrested.

On June 21, 1950 the patient was readmitted because of an increase in cough and expectoration.

Figure 2 shows the chest x-ray made at the time of readmission. It is noted that there was no change in the x-ray appearance since her first admission.

The readmission diagnosis was far-advanced pulmonary tuberculosis with doubtful activity, and chronic rheumatoid arthritis with secondary anemia. Laboratory findings showed 11 sputum

Fig. 2.—X-ray taken at the time of her readmission to the Sanatorium, June 21, 1950.

examinations to be negative for acid-fast bacilli; tuberculin skin test, positive, purified protein derivative (tuberculin) dilution 0.0001; red blood cell count 3,800,000; hemoglobin, 71%; white blood cell count, 3,100; sedimentation rate (Cutler method) 31; urine normal; Kahn test, negative.

From the Medical Department of the Missouri State Sanatorium, Mount Vernon, Mo.; resident physicians (Drs. Popp and Ottosen), and Superintendent (Dr. Brasher).

1. ATS Warns on ACTH and Cortisone Effect on Tuberculosis; Urges Tests, Bull. Nat. Tuberc. A. **37**: 4 (Jan.) 1951.
2. Tucker, W. B.: The Use of Drugs in TB Treatment, Bull. Nat. Tuberc. A. **37**: 21 (Feb.) 1951.
3. Spain, D. M., and Molomut, N.: Effects of Cortisone on Development of Tuberculous Lesions in Guinea Pigs and on Their Modification by Streptomycin Therapy, Am. Rev. Tuberc. **62**: 337 (Oct.) 1950.
4. Cortisone in Tuberculosis, Editorial, J. A. M. A. **145**: 907 (March 24) 1951.

For her pulmonary tuberculosis, bed rest was advised.

Because of severe pains in her joints, treatment with cortisone was started on Aug. 10, 1950. Dosage was as follows: 100 mg. every eight hours the first day; 100 mg. every 12 hr. the second day; 100 mg. the third day and thereafter. On Aug. 23, 1950, cortisone was reduced to 100 mg. every 48 hr. until a total of 2,500 mg. was given. During this course of cortisone from

Fig. 3.—X-ray taken on Oct. 27, 1950, showing cavity formation in the subapical region of the left lung.

Aug. 10, 1950, to Sept. 8, 1950, the patient's pulmonary condition showed no definite changes, as observed by fluoroscopy and clinical observation. Unfortunately, no chest x-ray was taken during this period because the patient did not show any symptoms of progression of her pulmonary lesion, nor did we have any knowledge, at that time, that cortisone could produce a reactivation of pulmonary tuberculosis. Clinically, the arthritis improved considerably, and the pain subsided almost completely after the third day of treatment. The anemia also improved, the erythrocyte count increasing to 4,400,000, and hemoglobin to 80%. Blood sugar and blood pressure remained within normal limits.

Three weeks after the first course was discontinued, severe rheumatic symptoms again developed in the patient, and a new course of cortisone was started on Sept. 27, 1950, the dosage being the same as in the previous course. In this second course the patient received a total of 1,500 mg. of cortisone. Again the patient's rheumatic condition improved rapidly, and her physical condition was satisfactory.

On Oct. 14, 1950, the patient had a moderate hemoptysis of about 6 to 8 ounces (0.18 to 0.24 L.). She was put on strict bed rest, and cortisone was discontinued. On Oct. 27, 1950, a chest

Fig. 4.—X-ray taken Jan. 27, 1951, showing marked improvement of the lesion in the left lung, with almost complete closure of the subapical cavity.

x-ray was made, which showed cavity formation in the subapical region of the left lung (Fig. 3). At the same time the patient had sputum examinations which were positive for acid-fast bacilli on direct smear. This was the first time in the patient's four-to-five year history of pulmonary tuberculosis that tubercle bacilli were found in her sputum.

Streptomycin, 1 gm. daily, and para-aminosalicylic acid (PAS), 8 gm. daily, were started on Oct. 27, 1950. There was no recurrence of hemoptysis.

An x-ray taken Jan. 27, 1951, showed marked improvement of the lesion in the left lung with almost complete closure of the subapical cavity (Fig. 4).

At the present the patient is still in the Sanatorium. A recent series of sputum examinations were negative for acid-fast bacilli. Her general condition and clinical findings referable to the chest are not suggestive of activity of her pulmonary tuberculosis.

COMMENT

The case reported suggests that an apparently arrested case of pulmonary tuberculosis has been activated by administering cortisone for arthritis. We feel justified in arriving at this conclusion because we have been unable to detect any other reasons for the reactivation, and the patient had no symptoms indicating activity of her pulmonary condition during the two-to-three-month period of observation prior to the administration of cortisone.

SUMMARY

A case of a 64-year-old white woman with pulmonary tuberculosis that was activated after receiving a total of 4,000 mg. of cortisone is reported.

DEVELOPMENT OF ACTIVE PULMONARY TUBERCULOSIS DURING ACTH AND CORTISONE THERAPY

Leo Fred, M.D., Melvin H. Levin, M.D., J. Bernard Rivo, M.D.
and
Thomas F. Barrett, M.D., Los Angeles

Of a group of patients with rheumatoid arthritis who had been receiving corticotrophin (ACTH) and/or cortisone in our arthritis clinic, clinical manifestations of active tuberculosis developed in one.

Because of the possibility that the appearance of fulminating clinical tuberculosis in this patient and the administration of the aforementioned widely used hormones were related rather than coincidental events, we consider it advisable to publicize this case history in detail.

REPORT OF A CASE

A white man aged 58, whose rheumatoid arthritis first became evident in January, 1949, was first admitted to Wadsworth Hospital in July, 1949, because of hepatitis. His arthritis was noted to improve markedly while he was jaundiced, but recurred with the subsidence of the hepatitis. A liver biopsy at that time was interpreted as demonstrating cirrhosis and superimposed hepatitis. He was discharged in October, 1949, and got along well until May, 1950, when he had a generalized exacerbation of his arthritis for which he was given combined vitamin C and desoxycorticosterone acetate by his private physician, which resulted in a marked aggravation of his symptoms with no objective changes. During May and June, 1950, he noted a low-grade fever and anorexia and a 20 lb. (9 kg.) weight loss, and therefore was admitted to Wadsworth Hospital again on June 20, 1950.

His family history is not significant. Previous to his present ailments, he had been well.

From the Medical Service, Wadsworth Hospital, Veterans Administration Center, Los Angeles, and the Department of Medicine, University of California at Los Angeles.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions of the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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Physical examination revealed a thin, poorly nourished white man who moved carefully and slowly with obvious pain on motion. His blood pressure was 110/70; his pulse was regular, and the rate was 70 beats per minute. His temperature was 100.2 F. There was limitation of motion of his neck and all peripheral joints, with increased heat, swelling, and tenderness of his proximal phalangeal, metacarpophalangeal, and ankle joints bilaterally. His liver edge was felt 4 fingerbreadths below the right costal margin and was nontender and smooth. Epitrochlear and axilliary glands were palpable. There was a subcutaneous nodule on the right upper arm. Several spider angiomas were noted over his upper thorax. His axillary and pubic hair was sparse. The rest of his examination was considered to be within normal limits. A roentgenogram of the thorax showed nothing significant (Fig. 1). Roentgenograms of the involved extremities revealed soft tissue swelling, but no gross bone changes except for generalized osteoporosis. The erythrocyte count was 4,450,000 with a hemoglobin value of 86%. The leukocyte count was 9,500, with 54% polymorphonuclear leukocytes, 36% lymphocytes, 5% monocytes, and 5% eosinophiles. The specific gravity of his urine was 1.023 with no abnormal constituents. The Kahn test was negative. The sedimentation rate (Wintrobe) was 22 mm. per hour. Blood urea nitrogen was 8 mg. per 100 cc., and serum uric acid was 2.3 mg. per 100 cc. The sulfobromophthalein test showed 8% retention in 45 minutes, thymol turbidity 17 units, and thymol flocculation 4+. Total serum proteins were 6 gm. with albumin 3.1 gm. and globulin 2.9 gm. Ketosteroids in urine specimens taken over a 24-hour period varied from 3.1 to 6.7 mg.

Because of daily temperature elevations varying between 100 and 101 F. with no new abnormal physical signs, urine cultures and blood cultures were done, with no growth demonstrated in any. A muscle biopsy revealed nothing significant, and a lymph node biopsy was reported as demonstrating nonspecific lymphadenitis. The subcutaneous nodule on his right arm was also subjected to biopsy and showed the typical changes of a rheumatoid nodule. A sternal marrow examination revealed a normal

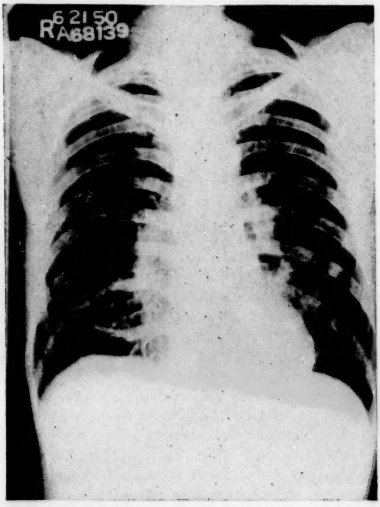

Fig. 1.—Chest roentgenogram of patient in case report taken 10 weeks before hormone therapy.

dispersion of marrow elements, and culture of the marrow was negative. Agglutination tests for typhoid, paratyphoid, and brucellosis were also negative.

The patient was considered to have active rheumatoid arthritis and chronic hepatitis with fibrosis. Since no other cause could be found for his fever, it was considered to be a manifestation of his rheumatoid disease, and treatment in this direction was instituted. He was given Δ^5 pregnenolone, 300 mg. daily, for two weeks with no subjective or objective improvement. Pregnenolone was then discontinued, and he was kept on acetylsali-

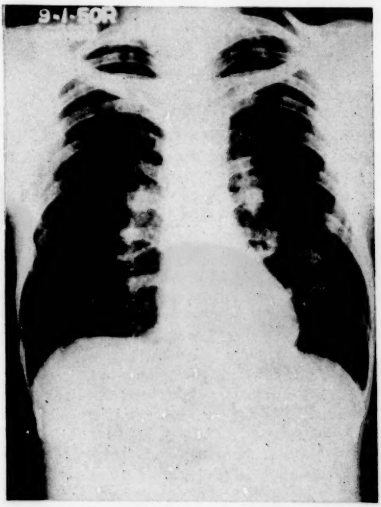

Fig. 2.—Chest roentgenogram taken the day hormone treatment began.

cylic acid, a high protein, high caloric diet, and paraffin baths for his affected extremities. There was mild improvement of his arthritis on this regimen, although his joints were still warm, swollen, and tender. He had no fever during this period. On Sept. 1, 1950, because of a slight nonproductive cough with no new physical signs on examination, a chest x-ray was taken (Fig. 2) which again revealed no abnormality. On this date, he was started on ACTH 20 mg. four times a day, and this was decreased to 15 mg. four times a day on Sept. 20, 1950. On Oct. 3, 1950, his temperature was 98.8 F., there was no objective evidence of arthritis discernible, he had gained 18 lb. (8 kg.), the sedimentation rate (Wintrobe) was 6 mm. per hour, the white blood count was 11,000 with a normal differential, and he felt very well. On Oct. 11, 1950, his temperature suddenly rose to 102.4 F. accompanied with a marked generalized exacerbation of his arthritis, a sedimentation rate (Wintrobe) of 32 mm. per hour, and a leukocyte count of 13,800, with 65% polymorphonuclear leukocytes, 30% lymphocytes, 3% monocytes, and 2% eosinophiles. At this time 100 mg. of cortisone was added to his 60 mg. of ACTH daily, after which he became afebrile and his arthritis improved again. However, on Oct. 20, 1950, his temperature again rose, this time to 104 F., his cough increased and became productive, and his arthritis became worse. ACTH was discontinued on this date, but he continued to receive 150 mg. of cortisone daily. On Oct. 31, 1950, an x-ray of his chest revealed an extensive inflammatory process in his right upper lobe (Fig. 3). He was considered to have pneumonia and he was started on procaine penicillin (crysticillin*) and aureomycin. His sputum, examined prior to antibiotic therapy, contained a mixed type of flora with no predominating organism and was not purulent. Two sputa concentrates were negative for acid-fast bacilli on Nov. 1, 1950. Blood cultures were negative. The spiking temperature continued. On Nov. 3, 1950, many colonies of Klebsiella, type B, were reported in his sputum, and therefore his therapy was changed to streptomycin and sulfadiazine. Blood cultures remained negative. He continued his febrile course, but did not appear or feel as ill as one would have expected, considering

the signs. On Nov. 8, 1950, cortisone was discontinued because it was felt that it might be adversely affecting his lung infection. X-rays revealed continuing extension of his pulmonary lesion. On Nov. 15, 1950, streptomycin and sulfadiazine were discontinued, and the patient was started on intravenous aureomycin.

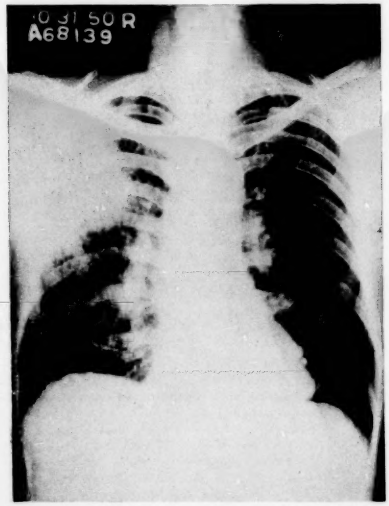

Fig. 3.—Chest roentgenogram depicting the findings immediately before hormone therapy was stopped.

After the cortisone was discontinued, his course seemed to go downhill quickly, and he appeared depressed and complained of increasing weakness and anorexia. On Nov. 16, 1950, his sputum was found to be loaded with acid-fast bacilli, but no Klebsiella organisms, and he was transferred to our Tuberculosis Section. Chest x-ray on Dec. 28, 1950 (Fig. 4), revealed early multiple cavitation. Recent sputum examinations have continued to show many acid-fast bacilli. He is now receiving streptomycin and para-aminosalicylic acid (PAS), with poor response thus far.

COMMENT

This patient, while receiving ACTH and cortisone, suddenly manifested clinical evidence of active pulmonary tuberculosis. His chest x-ray on Sept. 1, 1950, even on retrospective examination, revealed no abnormality, but a chest x-ray six weeks later showed extensive lung involvement which proved to be tuberculosis.

It is possible that this sequence of events had no relation to the administration of the hormones. He may have had latent tuberculosis (there is a Ghon focus in the left lower lung field) which became clinically active for unknown reasons, or he may have been reinfected during the time he spent next to a patient with tracheobronchial tuberculosis,[1] resulting in an acute fulminating type of tuberculous pneumonia which is prone to occur in patients already harboring chronic disease such as cirrhosis.

On the other hand, he was receiving hormones which, we are beginning to realize, may, among other effects, exert a powerful influence on the physiological reactions of the body to insult.[2] Present evidence suggests that these hormones, through some as yet unknown mechanism, have the ability to temporarily depress inflammatory response to injury, regardless of etiology.[3] This "antiphlogistic action," as Dougherty and Schneebeli call it,[4] probably explains the ameliorative effects of the hormones on the so-called collagen diseases, a group of disorders in which mesenchymal tissue hyper-reactivity, possibly secondary to noxious antibody stimulation [5] or other phlogogenic stimulus, is the main incapacitating element. (The release of this temporary depression of inflammatory reaction, which occurs when the hormones are discontinued, has in animals been followed by a rebound sensitized-tissue reaction more intense and destructive than the control sensitized-tissue response.[5] We think we have also observed this rebound phenomenon in man, and we expect to report our observations in detail at a later date. For example, after stopping the administration of ACTH or cortisone, in several of our patients a much severer grade of arthritis than they originally had flared up, and in one patient with rheumatoid arthritis who died six weeks after discontinuance of the hormones autopsy showed early fulminating disseminated periarteritis nodosa lesions which did not appear to be more than several weeks old. It therefore appears to us that the possibility of initiating or aggravat-

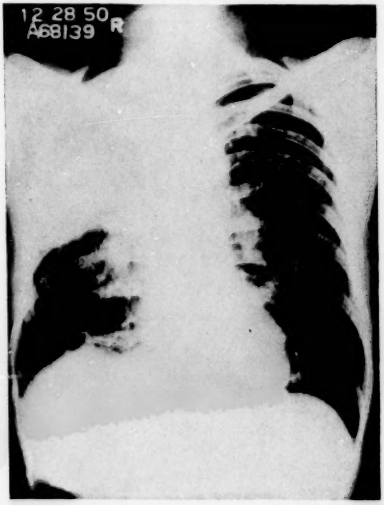

Fig. 4.—Chest roentgenogram showing the rapid progression of tuberculosis eight weeks later.

1. In August, 1950, this patient was in bed for one week next to a patient who was diagnosed later as having tracheobronchial tuberculosis.

2. Other effects noted while the patient was receiving the hormones were edema (relieved by 800 mg. sodium diet and parenteral mercurial diuretics), moon-face, diabetic glucose tolerance curve, mild euphoria, wound separation, and delayed healing of biopsy sites.

3. Gubner, R.: Therapeutic Suppression of Tissue Reactivity, Am. J. M. Sc. 222: 169 (Feb.) 1951.

4. Dougherty, T. F., and Schneebeli, G. L.: Role of Cortisone in Regulation of Inflammation, Proc. Soc. Exper. Biol. & Med. 75: 854 (Dec.) 1950.

5. Long, J. B., and Favour, C. B.: Ability of ACTH and Cortisone to Alter Delayed Type Bacterial Hypersensitivity, Bull. Johns Hopkins Hosp., 87: 186 (Sept.) 1950.

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ing human tissue hyperreactivity disorders with these hormones is one that deserves serious consideration.)

Concerning the suppressive effect of these hormones on allergic inflammatory response, Thorn [6] states that "ACTH or cortisone may dissociate the harmful effects of hypersensitivity from the beneficial reactions of immunity." However, it seems to us that this possibility should be viewed with great suspicion until there is definite evidence in its favor. The effect of these hormones on immune mechanisms is certainly not clear at the present time. For example, antibody levels have variously been reported increased,[7] unchanged,[8] and decreased,[9] following administration of adrenotropic or adrenocortical hormones. Also, the possible relationship between the lympholytic action of these hormones and antibody production or carriage, and the explanation for the reduction of serum gamma globulin [6] and the decrease in spleen size [10] following the administration of these hormones are still unknown. But even leaving aside possible hormonal influences on production or carriage levels of immune bodies, it is conceivable to us that this hormone ability to depress inflammatory reaction, although seemingly useful in the hyperreactivity disorders, could, paradoxically, harm the organ by interfering with what is still considered the body's first line of defense in those disorders in which inflammatory reaction seems to serve a useful service, as in infections. The physiological inflammatory reaction to a pathogen attempts to act not only as a physical barrier to the dissemination of the pathogen but also, to describe it simply, builds to the field of battle emergency lines of supply in the form of new blood vessels through which can flow a greater number of weapons such as macrophages and immune bodies. If this defensive effort is depressed by the hormones, we can visualize a situation, such as may have occurred in our patient, in which the invading organism, unaffected by the hormones,[11] continues to multiply,[12] and through its toxic products attacks and destroys tissue which can temporarily neither defend nor repair itself. Since inflammatory reaction is depressed, objective manifestations of inflammatory reaction products such as fever and increased sedimentation rate, may be diminished or absent, and the patient may, paradoxically, feel and look better in spite of continuing tissue damage.[13]

The effect of these hormones on specific infections has not been investigated to any great extent. Schwartzman has demonstrated the enhancing effects of cortisone and combined cortisone and ACTH on poliomyelitis infections in hamsters and mice. ACTH alone fail to produce this effect.[14] In humans, ACTH alone administered to patients already having poliomyelitis appeared to have no effect on the course of the disease.[15] One wonders, in the light of Schwartzman's work, what effect cortisone might have had. Perhaps the answer will be forthcoming during the next poliomyelitis epidemic if the supply of cortisone holds out. It is intriguing to attempt to associate the stress occurring in youngsters who overexercise with the frequent appearance in them of clinical poliomyelitis during epidemics. Could their increased adrenocortical output, perhaps through its lytic effect on fixed lymphoid tissue [16] with consequent release of enmeshed virus, or through some other unknown mechanism, be playing a part in activating the disease? Certainly, pregnant women, who have been shown to have increased adrenocortical activity, manifest a greater incidence of poliomyelitis than nonpregnant women. To theorize further, it is a common medical opinion that subclinical infections in general may become clinically evident when the "resistance" of the organism is lowered, as by chilling, anxiety states, overactivity, and other causes. Might it be that these resistance-lowering circumstances are stress situations which, if prolonged enough, increase adrenal cortical output to the extent of activating in some manner the sub-clinical infection?

Concerning bacterial infections, there is evidence that ACTH and cortisone may be capable of enhancing the susceptibility of tissues to the primary effect of bacterial toxins.[17] Mogabgab and Thomas found a marked enhancement of blood and tissue infection by Streptococcus hemolyticus in rabbits following injection of cortisone.[18]

In tuberculosis, Spain and Molomut [19] have shown that tuberculous lesions in guinea pigs receiving cortisone were more extensive, more widely distributed, and less well organized than in control groups. They feel that cortisone, through its inhibitory effect on formation of granulation tissue, inhibition of macrophage activity, and depletion of lymphocyte reserves, decreases resistance to progression of a tuberculous lesion. Tubercle bacilli in a rat, an animal which is normally resistant to tuberculosis as compared to the guinea pig and man who are naturally susceptible to tuberculosis, under the influence of cortisone are able to multiply more rapidly, produce more diffuse disease, disseminate widely, and result in

6. Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R., Jr.; Roche, M.; Staehelin, D., and Wilson, D. L.: Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**: 783 (May 18) 1950.

7. Dougherty, T. F.; Chase, J. H., and White, A.: Pituitary-Adrenal Cortical Control of Antibody Release from Lymphocytes: Explanation of Anamnestic Response, Proc. Soc. Exper. Biol. & Med. **58**: 135 (Feb.) 1945.

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death of the animal.[20] During the earlier investigations of the effect of these hormones in various disorders in humans, ACTH was administered to patients with active pulmonary tuberculosis, and although signs of inflammatory reaction products, such as fever and purulent sputum, were diminished, as one would expect, the lesions as seen on x-rays progressed.[13]

In attempting to account for the presence of live tubercle bacilli in the lungs of our patient, the possibilities seem to be (1) a latent infection, (2) reinfection with exogenous tubercle bacilli, (3) destruction of lung tissue by pneumonitis of pyogenic origin with the breaking up of old healed focuses still containing live bacilli, and (4) hormonal fibrolysis of old healed lesions with release of live tubercle bacilli. Concerning this last possibility, however, present evidence suggests that the adrenocortical hormones do not have a fibrolytic action, i. e., they have no effect on granulation tissue already formed.[19] It is impossible for us to state definitely which mechanism was involved in our case.

The Committee on Medical Research of the Trudeau Society recently warned of the use of ACTH and cortisone in patients with active tuberculosis or possible latent tuberculous infection.[21] They recommend routine diagnostic examination for tuberculosis of patients who are being considered for ACTH or cortisone therapy, a recommendation with which we heartily concur and to which we hope this report of our unfortunate patient will lend strong emphasis. However, we think this warning should include all infections, particularly those for which we have as yet no specific therapy, since we might not be able to put out the fire once we had stirred up its embers. Because of the suggestive evidence that these hormones might be hazardous, we have become extremely hesitant in administering them to patients for therapeutic purposes except as a last-resort measure. Perhaps we are being overcautious, but as clinicians we feel that we have no right to employ any form of therapy until it has been proved to be not only effective but also, and more important, not inimical to the welfare of the body.

SUMMARY

While he was receiving corticotrophin (ACTH) and cortisone for rheumatoid arthritis, active fulminant pulmonary tuberculosis developed in one of our patients.

The possible relationship between the administration of these hormones and the appearance of his tuberculosis, and infections in general, is discussed.

It is suggested that, until more information concerning the effects of these hormones is obtained, they should be used with extreme caution.

ADDENDUM

Since this paper was submitted for publication, the above patient died. At autopsy, bilateral caseo-cavernous tuberculosis and confluent tuberculous pneumonia were found. Additional findings were rheumatoid arthritis and hepatic cirrhosis.

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Other examples of complicating infections proved at autopsy in patients receiving these hormones are as follows:

1. Diffuse purulent meningitis developed in a patient with multiple myeloma.

2. A patient with acute lymphatic leukemia died with acute disseminated actinomycosis.

3. A patient treated for stasis dermatitis was found to have miliary tuberculosis.

The detailed report of these cases will be published at a later date.

SARCOIDOSIS BENEFITED BY PREGNANCY

REPORT OF A CASE

Robert H. Berman, M.D., Detroit

A review of many textbooks of medicine and of obstetrics revealed no mention of pregnancy in sarcoidosis. There have been, however, some reports of pregnancy in the remission or quiescent stage of the disease. The removal of the spleen in a patient in the fifth month of pregnancy complicated by purpura has been reported.[1] The sarcoidosis was apparently not suspected until the spleen was sectioned. No other evidence of sarcoidosis was noted. The pregnancy terminated normally. In the same article, another similar case was briefly mentioned in the discussion. Dr. Warfield T. Longcope stated that he had not found any pregnant patient with active sarcoidosis in the large series of cases he had studied. He mentioned, however, that one of his patients did have two successful pregnancies after what appeared to be recovery from a rather extensive sarcoid involvement of the lungs.[2] In a clinical review of 11 cases of sarcoidosis, three of the four female patients described had had pregnancies. Two had full-term pregnancies; one, a miscarriage.[3] The case histories, however, gave no indication as to whether the pregnancies occurred before or during the sarcoid involvement. Recently there was a report of a patient with sarcoidosis who had two pregnancies.[4] The first pregnancy was aborted, and the second was allowed to go to full term. The sarcoidosis in the second was apparently in a quiescent stage and was not affected by the pregnancy.

The case presented here appears to be the first reported of a sarcoid patient with two full-term pregnancies, where, at least in the second pregnancy, the sarcoidosis appeared to be in an active stage.

REPORT OF CASE

The patient, then 20 years old, complained in September, 1939, of "flashes in eyes." Examination disclosed iritis. The white blood cell count was 6,950 and the differential count was normal, with 1% eosinophils. Chest x-ray and tuberculin test

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4. Russel, K. P.: Sarcoidosis (Boeck's Sarcoid) and Pregnancy, Bull. Moore White Clin., p. 14, 1950.

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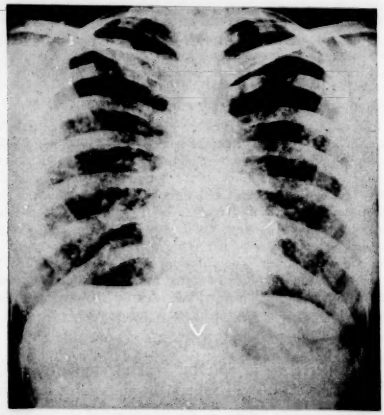
were negative. The patient was referred for ophthalmological examination, and iritis and conjunctivitis of uncertain origin were reported. In 1941 a chest x-ray taken elsewhere disclosed bilateral lung involvement, which was thought to be moniliasis. Repeat films in 1942, 1943 (Figure), and 1945 showed little change.

In May, 1946, the patient had a child. She consulted me in May, 1947, because of acute chest pain and cough. Fine crepitant rales, scattered through both lungs, were heard. The spleen at this time was greatly enlarged. Chest films showed little change from 1942. She was seen at Mayo Clinic in August, 1947, where the diagnosis of sarcoidosis was made and confirmed by inguinal gland biopsy. In September, 1947, the spleen extended almost to the umbilicus and to the left anterior superior spine. Dr. Paul S. Barker, professor of medicine at the University of Michigan Medical School, suggested that calciferol be tried in the dosage used in the University Hospital.

In February, 1948, a month after calciferol was started, the patient was found to be over three months pregnant. Decision to allow pregnancy to proceed was made with much concern, but the spleen receded, vomiting stopped, and pregnancy proceeded normally, with the patient subjectively well throughout. By the eighth month of pregnancy the spleen was palpable only on deep inspiration. Spleen percussion also showed the decreased



Roentgenogram of chest taken in 1943, showing extensive infiltration of both lungs.

size. X-ray of the lungs remained unchanged. In June, 1948, the total serum protein was 7.19 gm., with albumin 2.65 gm., and globulin 4.54 gm.

On Aug. 12, 1948, the day before her delivery, the total serum protein was 4.98 gm., with albumin 3.16 gm., and globulin 1.82 gm., a return to normal ratio. The patient was delivered of a healthy 6-lb. (2.7 kg.) girl by Dr. Albert E. Catherwood, at Harper Hospital, Detroit. The spleen, soon after delivery, was barely palpable after deep inspiration. On the third day it was palpable without inspiration. Soon after breast feeding was stopped, the patient began to again have cough and dyspnea. She stated that the same order of events occurred in her first pregnancy. A chronic cough disappeared soon after the start of that pregnancy; she was excellent during pregnancy and lactation, but began to have symptoms afterward.

In December, 1948, the spleen again reached almost to the umbilicus and to the left anterior superior spine. The same month in her home she was in close contact with a worker who had advanced pulmonary tuberculosis. In February, 1949, she became acutely ill with cough, fever, and marked dyspnea. No acid-fast bacilli were found in the sputum. The total serum protein was 6 gm., with albumin 3.1 gm., and globulin 2.9 gm. She complained of severe abdominal pain and diarrhea. A moderate cough and morning sputum continued, and there was a slight, but constant, weight loss. In June cyanosis of lips and fingertips appeared. The cough and cyanosis were relieved only by oxygen. On June 25, 1949, sputum showed acid-fast bacilli. A tuberculin test the next day showed a positive reaction. Specimens the next two days were again positive. The roentgen report by Dr. Lawrence Reynolds on chest film of July 5, 1949, was "The lesions of the chest at this time are of the miliary character and have every appearance of being changes incident to miliary tuberculosis."

The patient's weight was now 85 lb. (38.6 kg.), instead of her normal 110 (49.9 kg.). She was placed in the Detroit Tuberculosis Sanatorium and her symptoms abated under daily streptomycin therapy. After four weeks moderate vertigo and mild urticaria appeared. A change to dihydrostreptomycin did not ameliorate the vertigo and urticaria. She was placed on a regimen of streptomycin, 1 gm. every third day. The vertigo disappeared. Slight urticaria persisted. Para-aminosalicylic acid, 9 gm. daily, was added. On Nov. 21, 1949, the Robinson-Power-Kepler test was positive in both urine and blood, and seemed to support the clinical suspicion of Addison's disease. The 24-hour urine assay showed diminished 17-ketosteroids, 3.8 mg., suggesting adrenal involvement. In February, 1950, the eosinophil test was done. The white blood cells showed a drop from 5,300 to 5,050, and the circulating eosinophils from 80 per cubic millimeter to 25 per cubic millimeter, after epinephrine. This indicated normal adrenal cortex response. The possibility of an intermittent Addison status was considered. The patient's weight April 2, 1950, was 109 lb. (49.4 kg.). Spleen remained enlarged. Sputa examinations on April 2, and April 20 were negative. A chest film on April 28, 1950, showed a change from a miliary character to that of a bilateral fibrosis. The patient's status and findings have remained the same to Sept. 1, 1950.

COMMENT

The most important feature in this case was the patient's excellent status, judged from the patient's own statement, during her first pregnancy, and improvement noted by me in her second pregnancy. The improved clinical state and the reduction in spleen size to normal during the second pregnancy suggested a benefit from the pregnancy. The reversed albumin-globulin ratio of the serum proteins, often found in sarcoidosis, became normal in the latter part of the pregnancy and also suggested improvement. On the other hand, the lung infiltration did not change, and the tachycardia persisted. The latter might possibly be due to sarcoid involvement of the heart, despite negative cardiac findings throughout.

It has long been apparent that pregnancy exerts a neutral or favorable influence in many diseases. The improvement in atrophic arthritis by compound E (17-Hydroxy-11-Dehydrocorticosterone)[5] suggests the benefits in pregnancy may be due to the increased elaboration of compound E or of hormones with similar effects. The favorable effect of pregnancy on peptic ulcer has been considered as possibly due to hormonal factors.[6] The favorable effect of pregnancy on some diabetic mothers may be due to insulin from the hypertrophied islets of the fetus.[7] In Addison's disease, pregnancy usually exerts an

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unfavorable effect. When the patient improves during pregnancy, compensatory hypertrophy of the fetal adrenal cortex is postulated.

The involvement of the lymphoid system in sarcoidosis makes it tempting to consider adrenal involvement as a possible cause of sarcoidosis. The value of adrenal cortex factors in diminishing enlarged spleens and lymph glands in other diseases has been recently noted.[8] Calciferol and dihydrotachysterol as therapeutic agents appear to be valuable in sarcoid therapy. The close relation of these drugs to the adrenal and ovarian steroids seems significant. In this case trial of corticotrophin (ACTH) was considered, but was delayed because of the tuberculosis.

The possibility of coincidental temporary improvement in the sarcoidosis with the pregnancies and during lactation cannot be denied. It is obvious that one must be wary of conclusions from a single case. The fact, however, that improvement occurred in both pregnancies appears significant.

CONCLUSIONS

A patient with sarcoidosis had two normal full-term pregnancies, with improvement in the sarcoid status during the pregnancies.

The hormonal changes evoked by pregnancy may be a clue to the etiology and treatment of sarcoidosis.

1304 David Broderick Tower.

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TREATMENT OF SALMONELLA SEPTICEMIA WITH CHLORAMPHENICOL

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This is a report of a case of Salmonella septicemia without gastrointestinal symptoms successfully treated with chloramphenicol (chloromycetin®).

REPORT OF A CASE

E. L., a 27-yr.-old Negro woman, entered the Central Free Dispensary of the Presbyterian Hospital on Aug. 7 with complaints of severe parietal headache, sore throat, pain in the low back, and cough of one week's duration. In the week prior to her admission she suffered two episodes of severe shaking chills and high fever. Her throat was sore; she could not swallow solid foods, and she had been lethargic for a week. No history of diarrhea or gastrointestinal upset was elicited, and the systemic review indicated essentially normal conditions except for pain in the chest when coughing. This cough was productive of small amounts of yellowish sputum. A diagnosis of chronic pelvic inflammatory disease was made in this clinic two years before her present admission.

Physical examination revealed a small 27-yr.-old Negro woman who appeared acutely ill. Her temperature was 102 F. and her pulse rate 120 and regular. The abnormalities found were markedly reddened tonsils and pharynx, a soft systolic murmur over the entire precordium, tenderness in the lower abdomen, and tenderness and enlargement of the left Fallopian tube on pelvic examination.

Laboratory Findings.—The erythrocyte count was 3,890,000, with 12 gm. of hemoglobin, and the leukocyte count was 3,500, of which 78% were polymorphonuclears and 22% lymphocytes. The Kahn reaction was negative, and the urine examination findings were normal. The blood sedimentation rate was 44 mm. an hour (Wintrobe). Three successive negative stool cultures were reported. Streptococci of the viridans group were recovered from a throat culture. X-ray examination revealed no abnormalities in the heart or lungs, and the electrocardiogram was normal. Cultures of blood drawn on the first, second, and third days of the patient's illness showed pure cultures of a gram-negative bacillus which produced acid, gas, and hydrogen sulfide in Kligler's medium; no fermentation in Endo agar, and no fermentation in lactose and saccharose mediums and failed to liquefy gelatin or produce indole. There was no agglutination by paratyphoid serums A or B. In the Illinois State Department of Health Laboratory the organism proved to be salmonella Montevideo by slide agglutination with nonspecific antiserums. Agglutinations with typhoid antiserums were negative. Qualitative sensitivity tests revealed that chloramphenical completely inhibited the growth of this organism. There was no growth retardation by aureomycin, streptomycin, penicillin, or sulfadiazine.

Clinical Course.—On the day of admission the patient was given 600,000 units of procaine penicillin G for aqueous infection (crysticillin®), which was continued for two days with no change in the temperature or the symptoms. After blood cultures revealed S. Montevideo infection, chloramphenicol was administered in doses of 250 mg. every four hours after an initial dose of 1 gm. Twenty-four hours later the patient was afebrile, and her symptoms subsided. The systolic murmur heard on admission was softer. The chloramphenicol was continued for four days with a total dose of 6 gm. Two weeks following cessation of treatment the patient was afebrile and asymptomatic. Repeated blood and stool cultures were negative.

COMMENT

It is interesting to note the striking similarity of the infection in this case to Salmonella suipestifer infection. Harvey [1] in 1937 reviewed the literature of S. suipestifer and reported 21 new cases. He stated that in the majority of his cases there was an uncomplicated bacteremia simulating typhoid. He found that the organism was readily cultured from the blood but rarely from the stools. Forty-four of the 71 cases that he reported or reviewed were without localizing signs of infection. Goulder, Kingsland, and Janeway [2] reported 11 cases of S. suipestifer with one case of endocarditis due to this organism. Their cases also showed a typhoidlike infection without localizing signs of infection.

S. Montevideo was first isolated in Uruguay from lymph nodes of healthy swine and later from infants with summer diarrhea by Hormaeche and others.[3] They found the organism to be from the VI and VII groups, with flagellar antigens related to those of S. enteritidis and S. Senftenberg, without being identical with either of them.

This organism also has been found in the stools of chicks and human beings.[4] The greatest animal reservoir of S. Montevideo is probably in domestic fowl.[4]

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1. Harvey, A. M.: Salmonella Suipestifer Infection in Human Beings: Review of Literature and Report of 21 New Cases, Arch. Int. Med. **59**: 118 (Jan.) 1937.

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Edwards and Bruner [5] have found it in 17 out of 325 food-poisoning outbreaks in man in the United States between 1934 and 1941.

An epidemic of S. Montevideo food infection was reported in 1944 by Myers and Eckles.[6] In this epidemic 975 men became ill with fever, diarrhea, nausea, vomiting, and headache. None of these patients died, and most of them were discharged after 96 hr. with few or no symptoms.

In the period from April, 1939, to the close of 1945 about 2,000 Salmonella infections were identified by the New York Salmonella Center.[7] Cultures came from many parts of the United States and some adjoining territories. Of these 2,000 cases of Salmonella infection, 134 proved to be due to S. Montevideo. In the literature of the established cases of S. Montevideo no case has been reported in which a septicemia occurred without gastrointestinal symptoms.

Because of the associated murmur there is an unproved possibility that this case is one of Salmonella endocarditis. A case of this disease caused by S. Minnesota with no demonstrable primary focus was reported by Kurz, Crehan, and Thomson.[8] In that case no improvement was effected by sulfadiazine, penicillin, or streptomycin, and the patient died.

This case demonstrated dramatic clinical response to chloramphenicol therapy, and a qualitative sensitivity test showed that growth of the organism was completely inhibited by this drug and not by other antibiotics.

Chloramphenicol has been employed successfully by Ross and others [9] in the treatment of S. enteritis, but none of their cases was complicated by septicemia.

Although there is no established link, two possible foci of infection are suggested, namely, the pharyngeal and pelvic infections. The pharyngeal infection was a prominent part of the clinical picture, but the culture revealed only streptococci of the viridans group. Infection from a pelvic focus not infrequently is due to the Salmonella group, and there is evidence here of chronic inflammatory disease of long standing. However, there is no proof of a bacteriologic relationship in this case. There is also no evidence of a focus in the intestine.

SUMMARY

An instance of S. Montevideo septicemia without gastrointestinal symptoms successfully treated with chloramphenicol is described; the similarity of this case to cases of S. suipestifer infection is suggested, and the characteristics, incidence, and bacteriology of the organism are discussed.

1753 W. Congress St.

5. Edwards, P. R., and Bruner, D. W.: Occurrence and Distribution of Salmonella Types in the United States, J. Infect. Dis. **72**: 58 (Jan.-Feb.) 1944.

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9. Ross, S., and others: Chloromycetin in the Treatment of Salmonella Enteritis, New England J. Med. **242**: 173 (Feb. 2) 1950.

USE OF CHLORAMPHENICOL AND TYPHOID VACCINE IN INFANT BORN OF TYPHOID CARRIER

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In the course of routine epidemiological studies made since 1934 on all food handlers, professional personnel, and patients in the obstetric and pediatric services of the Bronx hospital,[1] the staff was recently confronted with the problem of a newborn child delivered by a previously undiscovered typhoid carrier. This case report is concerned with bacteriologic and serologic studies of mother and infant and with the prophylactic use of chloramphenicol and vaccination for protection of the baby.

REPORT OF CASE

M. A., a 25-yr.-old nullipara, was admitted to the antepartum clinic on June 9, 1949. Her last menstrual period was on Jan. 20, 1949. The patient had been in a German concentration camp and had experienced recurrent episodes of cholecystitis during the period 1946-1948. Her prenatal care progressed normally, and she was admitted to the Bronx Hospital on Nov. 7, 1949, in active labor. At 1:05 p. m. she gave birth spontaneously to a living male child. Routine stool examination done on admission, Nov. 9, 1949, was reported positive for Salmonella typhosa, and mother and child were isolated. Agglutination tests for the mother done on Nov. 10 were positive for Salmonella typhosa H antigen in a dilution of 1:10 and for Vi antigen in a dilution of 1:16. Confirmatory fecal studies were made at Bronx Hospital on Nov. 15 and Nov. 18 and several times by the New York City Department of Health. Aspirated duodenal contents also revealed S. typhosa in great numbers, indicating the gall bladder or hepatic ducts as the reservoir of infection. The patient had no physical complaints, and her postpartum convalescence was uneventful.

The male infant was admitted to the nursery on the day of delivery in good physical condition and was transferred to the isolation ward two days later when the positive fecal culture of its mother was revealed. On Nov. 10 the agglutination tests for S. typhosa O and H antigen were negative; the blood count was as follows: hemoglobin 16.2 gm.; erythrocytes 5,000,000 per cubic millimeter; leukocytes, 6,000 per cubic millimeter, with a differential of lymphocytes 75%, segmented forms 18%, eosinophils 2%, and monocytes 5%. Fecal cultures from Nov. 10 through Nov. 18 were negative for Salmonella and Shigella organisms. A blood culture on Nov. 21 proved sterile and a blood count on the same day was normal. On the third hospital day, Nov. 9, 1949, the child began to receive chloramphenicol, 250 mg. per day. On Nov. 14, six days later, administration of the antibiotic was discontinued because of anorexia. After this, the child did well and was discharged on Nov. 22, 1949.

On Dec. 1, 1949, the infant was readmitted for immunization. Physical examination revealed no abnormality. Routine urinalysis elicited negative findings. Blood agglutination studies for typhoid were negative. Subsequent numerous fecal cultures for Eberthella typhi made over the period from Dec. 2, 1949, to April 1, 1950, were all negative. The Wassermann and Kahn tests were negative.

On Dec. 2, 1949, the patient received 50,000,000 organisms of a stock monovalent typhoid vaccine of wide antigenic pattern; a second dose of 100,000,000 was administered on Dec. 16; a third

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Dr. A. J. Weil, Bacteriologist, supplied help and advice in the bacteriologic and serologic examinations. These studies were made possible by the permission of Drs. M. Rosensohn, Director of Obstetrics; A. C. Posner, Attending Obstetrician, and J. Lapin, Attending Pediatrician.

1. Felsen, J., and Wolarsky, W.: The Hospital Epidemiologist, Hospitals **14**: 41 (Aug.) 1940.

dose of 150,000,000 was given on Dec. 23, and a fourth of 200,000,000 on Dec. 30. No reactions occurred, and the infant was discharged for follow-up in the outpatient department.

On Jan. 6, 1950, the infant received 250,000,000 organisms, resulting in a reaction characterized by fever, anorexia, and irritability. Immunization was discontinued. Repeat blood agglutination titers for typhoid O and H antibodies on Jan. 23 and April 1, 1950, were entirely negative. Frequent physical examinations of the infant during this period revealed an occasionally, not persistently, palpable spleen, but no other abnormality.

COMMENT

In an evaluation of the prophylactic use of chloramphenicol and the serologic implications of these studies, certain known facts had to be borne in mind. For example, there is no evidence that there is any transplacental transmission of protective antibodies against Salmonella or Shigella infection from mother to infant.[2] Indeed, the newborn are very susceptible to these infections, and the mortality rate is high.[3] The chances of the infant's being infected are also high, since the fetal head crosses the perineum, which is often soiled by intestinal contents of the mother. In some cases the obstetrician may transmit the infection by means of his soiled gloves. In either case it is an "intestine to mouth" infection. In this case, the absence of typhoid organisms in the blood of the newborn was ascertained; hematogenous dissemination through the placenta had not occurred.

Chloramphenicol is transmitted through the placenta from mother to infant without toxic manifestations.[4] It therefore appears feasible, when the mother is known to be a typhoid carrier, to administer chloramphenicol before term, for the protection of the fetus.

The effects of active immunization could not be proved by our serologic studies, since demonstrable protective or other antibodies are not readily elicited in the newborn.

On the basis of these studies, we can conclude only that an infant born of a typhoid carrier had every chance of becoming infected but did not do so, possibly because of the prophylactic use of chloramphenicol and active immunization. The mother has been urged to undergo cholecystectomy on the supposition that the gall bladder may be the sole repository for her residual infection and, more particularly, since the positive fecal cultures have persisted in spite of chloramphenicol therapy. The question naturally arises at this point, if the organism is resistant to chloramphenicol therapy in the mother, how could the same antibiotic be effective in the infant? It is possible that the drug may be more effective when used before mass infection has occurred.

SUMMARY

A case is presented of an infant born of a mother who proved to be a typhoid carrier. Prophylactic use of chloramphenicol and active immunization in the infant and associated serologic studies are described.

16 Church Street.

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BUREAU OF LEGAL MEDICINE AND LEGISLATION

MEDICOLEGAL ASPECTS OF ARTIFICIAL INSEMINATION

There is little that can be said with any degree of assurance concerning the medicolegal aspects of artificial insemination for such aspects have not been explored satisfactorily by any court of appellate jurisdiction in the United States. Yet, the procedure is no longer novel. It was reported (*J. A. M. A.* **116**:2747 [June 21] 1941) that by 1941 almost 10,000 pregnancies had occurred in the United States as a result of this procedure. Physicians and lawyers alike seek answers to the many questions that may arise concerning a situation not known to the common law and not now covered by specific statutory provisions, questions relative to legitimacy, to inheritance, and to liability in connection with the selection of donors, among others.

PHYSICIAN'S LEGAL RESPONSIBILITY

If the donor is the husband of the woman inseminated artificially, the application of the ordinary laws relating to malpractice will probably be sufficient to protect the rights of all parties. The child, if one results, will unquestionably be legitimate, and, if the physician exercises due diligence, uses ordinary knowledge and skill and his best judgment, and respects the confidence of his patient, he will not be liable for damages even though the resulting baby be defective. What constitutes due diligence, ordinary knowledge and skill will depend on the accepted practice at the time in the community in which the artificial insemination is performed or in a similar community among physicians engaged in or holding themselves out as ready to engage in the artificial insemination of would-be mothers.

When the physician uses semen from a donor other than the husband, there is a possibility that complications may arise. In such cases the law must be applied to a novel situation, but certainly the physician assumes a certain degree of responsibility as to the suitability of the donor. In selecting a donor, or in passing judgment on the fitness of a donor offered by a woman who wishes to be artificially impregnated, or by her husband, the physician assumes responsibility the nature and limits of which have not been determined by statutory law or defined by the courts.

What the law requires of him in the way of investigation of the suitability of a prospective donor, from the standpoint of heredity and present phyiscal condition, and how far he will be held liable for errors of judgment in vouching for the fitness of the proposed donor, no one can say with any degree of certainty.

How far the courts will recognize a right on the part of a woman who is to be inseminated and of her husband, to assume by express contract the risks of unsatisfactory results due to the unfitness of the donor is impossible to say. A patient may by express agreement relieve a physician of some of the obligations imposed on him by the usual implied contract for medical services, but not all of such obligations. How far the law will permit a woman or her husband to assume the risks of the fitness of a donor, which is a matter that is or should be peculiarly within the knowledge of the physician, is uncertain.

ADULTERY—LEGITIMACY

Because criminal statutes are strictly construed it is doubted by some that a medical procedure such as this, performed privately with the consent of all concerned, violates statutes relating to adultery or rape. In support of this view it is pointed out that statutes concerning adultery use phrases such as "if any man and woman shall live together in an *open* state of adultery" or the words "open," "notorious," "cohabit" or the like. In this procedure there is no cohabitation between man and woman not married to each other and there is no openness or notoriety associated with it. There is no carnal knowledge of a woman as that term is used in law. The procedure, a medical one designed to cause conception, lacks the elements of lust, passion or force. There is an absence of a physical, sexual relationship between man and woman. It is also pointed out that statutes relating to

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adultery and rape apply to natural physical acts whereas this procedure as its name acknowledges is artificial.

Others believe that the operation does constitute adultery. It is said that a child which results from heterologous artificial insemination is conceived outside of the marriage relation and is not the child of a wife and her husband. It is further stated that this procedure is unlawful as against public policy and that consent to such unlawful act can not be valid nor can it make the act lawful.

A child born in lawful wedlock is presumed to be legitimate. Because a child conceived as the result of a heterologous artificial insemination of a married woman with the consent of her husband is born in lawful wedlock, one school of thought believes that the child so conceived should be considered and is legitimate. This group reasons that consent by both husband and wife to the procedure is a valid exercise of a right incident to the marriage relationship to accomplish one of the ends of marriage. It is also reasoned that because there is no express prohibition in law against this procedure the resulting child is legitimate. This group does not make clear what the status of a child would be were it conceived in the absence of the husband's consent, although it is implied that it would be illegitimate.

Another school of thought holds that the procedure is unlawful in itself because it is artificial and contrary to nature and thus against public policy. This group believes that the child is unlawfully conceived and therefore is not legitimate. This group advocates that adoption proceedings be completed to protect the rights of a child so conceived or that statutes relating to the procedure itself and to the rights of the child be adopted.

In civil law it may well be doubted that a child so conceived even with consent, would satisfy a requirement of will or deed requiring for its execution "lawful issue of his body" or "heirs of his blood." It may be questioned whether such issue is the grandchild of the paternal grandparents.

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COURT CASES

In a Canadian case decided in 1921, *Orford v. Orford, 49 Ontario Law Reports 15,* there was involved an alleged case of artificial insemination, performed in England on a woman whose husband was in Toronto, Canada. While the question was not definitely determined by the court, it was strongly intimated that a woman who submits to an artificial insemination without the consent of her husband, the donor being a man other than her husband, commits adultery. The court in its dicta described adultery as "the voluntary surrender to another person of the reproductive powers or faculties of the guilty person."

Another case arose in New York in 1947, *Strnad v. Strnad, 78 N.Y.S. (2d) 390.* The court had granted a decree of separation to a wife and in that decree authorized the husband to have custody over the weekends of a child born to the wife. The wife subsequently asked the court to amend the decree on the ground that the child resulted from an artificial insemination, the donor being a person other than the husband, and therefore the husband was not the father of the child. In the written opinion of the Supreme Court of New York County, New York, it was said:

"The court has assumed, for the purpose of this litigation in the light of the record and the concessions made by the defendant, that the plaintiff was artificially inseminated with the consent of the defendant and that the child is not of the blood of the defendant. Predicated on that assumption the court concludes as follows:

"(1) . . .

"(2) The court holds that the child has been potentially adopted or semi-adopted by the defendant. In any event, in so far as this defendant is concerned, and with particular reference to visitation, he is entitled to the same rights as those acquired by a foster parent who has formally adopted a child, if not the same rights as those to which a natural parent under the circumstances would be entitled.

"(3) In the opinion of this court, assuming again that the plaintiff was artificially inseminated with the consent of the defendant, the child is not an illegitimate child. Indeed, logically and realistically the situation is no different from that of a child born out of wedlock who by law is made legitimate upon the marriage of the interested parties.

"(4) The court does not pass on the legal consequences in so far as property rights are concerned . . . nor does the court express an opinion on the propriety of procreation by the medium of artificial insemination. . . ."

In an English case, *L. v. L.,* [1949] *1 All E. R. 141,* decided Nov. 30, 1948, (Probate, Divorce and Admiralty Division) a decree of nullity was granted to a wife on the ground of her husband's incapacity to consummate the marriage, although the wife had borne a child after having been artificially inseminated with her husband's semen. Evidence established that the husband was psychologically unable to have normal sexual relations with his wife. It was further established that he had consented to the artificial insemination to satisfy his wife's desire for a child and her hope that normal relations might be established. Although the marriage was set aside as null and void and the child held to be illegitimate, this case can only be taken as authority for the principle that the artificial insemination of a wife with her husband's semen, normal intercourse being impossible, did not, under English law, consummate a marriage.

LEGISLATION

No legislation has been enacted in any of the states which deals specifically with the several aspects of artificial insemination. Since 1948, however, bills have been introduced in the legislatures of five states dealing with the rights of a child born following an artificial insemination.

A New York bill (S. 745) provided as follows:

"A child born to a married woman by means of artificial insemination with the express or implied consent of her husband shall be deemed the legitimate, natural child of both the husband and his wife for all purposes, and such husband and wife and such child shall sustain toward each other the legal relation of parent and child and shall have all the rights and be subject to all the duties of that relationship including the rights of inheritance from each other."

This bill failed of enactment. Another bill (S. 587) containing the provision similar to the quotation plus a further provision that consents for this procedure should be filed with the county clerk was introduced in the New York Senate in 1950. It, too, failed of enactment.

A proposal (S. 199) was submitted in 1948 to the Virginia legislature. This bill, which was not enacted, provided simply the children born as a result of artificial insemination should be considered the same as legitimate children for all purposes if the husband of the mother consented to the operation.

In 1949 bills were introduced in Wisconsin (Assembly Bill 407), Indiana (H. B. 350) and Minnesota (H. B. 1090, 1091, 1092 and S. B. 1108, 1109 and 1110). None was enacted into law. The Wisconsin and Indiana bills declared a child so conceived to be legitimate and to have full rights of inheritance. In addition the Indiana bill provided that the physician and the mother of the child should retain copies of consent to the procedures while the Wisconsin bill provided that such consent would have to be filed with the registrar of probate. In Minnesota three bills were introduced in the House and three companion bills were introduced in the Senate. One pair provided that artificial insemination was unlawful but that children so conceived were legitimate; another provided that artificial insemination was lawful if the husband's semen alone was used; and the other provided that artificial insemination was a lawful procedure. Provisions regulating and controlling the performance of the operation were established: mother and donor would have to be free of a disease, affliction or imperfection likely to be communicated to or inherited by the child; the doctor must be of the opinion that the donor resembles husband in physique, appearance and temperament and that donor's and donee's blood are compatible; donors may not be nearer in kin to the donee than second cousins.

The Sanitary Code of the City of New York was amended, effective July 1, 1947, to impose certain restrictions on the use of donors for artificial insemination. This amendment, and the regulations issued pursuant to it, required, among other things, that a donor be given a complete physical examination; that donors found to be suffering from specific conditions may not be used; that the blood of the donor and donee be typed with respect to the Rh factor; and that the physician performing the operation prepare records showing compliance with these requirements.

MEDICOLEGAL ARTICLES

There have been a number of articles written on the medicolegal aspects of this procedure. Reference to them with brief description of their content follows:

Abel, S.: The Present Status of Artificial Insemination, Surgery, Gynecology and Obstetrics, December, 1947. (Surgical Publishing Co., 54 E. Erie St., Chicago.) Dr. Abel, of the Department of Obstetrics and Gynecology at Northwestern University Medical School, discussed not only the legal aspects of artificial insemination but also its theological aspects and includes a suggested draft of a law dealing with the legitimacy of the issue of children so conceived.

Tucker, F. B.: Legal Problems of Artificial Insemination, Woman Lawyers Journal, Spring, 1947. (National Association of Women Lawyers, 80 Federal St., Boston 10.) Miss Tucker, of the Chicago, Illinois, Bar, discusses the physician's duties and responsibilities in artificially inseminating a married woman; points out legal pitfalls to be wary of; and comments on the need for legislation covering this subject.

Seymour, F. I., and Koerner, Alfred: Medicolegal Aspects of Artificial Insemination, J. A. M. A. **107:***1531 (Nov. 7) 1936.* (American Medical Association, 535 No. Dearborn St., Chicago 10, Illinois.) Drs. Seymour and Koerner discuss the legal unknowns in the subject of artificial insemination and emphasize the responsibility of the physician "not only in the creation of the child but in its future welfare, particularly in its adjustment to its own family unit."

Seymour, F. I., and Koerner, A.: Artificial Insemination, Present Status in the United States as Shown by a Recent Survey, J. A. M. A. **116:***2747 (June 21) 1941.* The authors analyze the means and results of artificial inseminations resulting in 9,489 pregnancies, 97 per cent of which resulted in the birth of live babies. While the article is statistical and entirely medical, it may be of interest to lawyers and legislators who desire to compare the percentage of medical complications arising from artificial insemination with those occurring in natural pregnancies.

Greenhill, J. P., and Wright, J. F.: Artificial Insemination: Its Medicolegal Implications, A Symposium: American Practitioner, January, 1947. (Also found in "Symposium on Medicolegal Problems," Ed. S. A. Levinson, Published by J. B. Lippincott, Philadelphia, in 1948.) Dr. Greenhill, Professor of Gynecology at Cook County Post-Graduate School and Mr. Wright of the Chicago, Illinois, Bar Association presented talks concerning both the medical and legal history and medical and legal problems of artificial insemination at a meeting of physicians and lawyers under the co-sponsorship of the Institute of Medicine of Chicago and the Chicago Bar Association. A transcript of the discussion afterwards contains questions of practical interest posed by medical and legal practitioners. The answers emphasize practical medical and legal problems, and suggest various solutions.

Foreign Letters, Paris, Artificial Insemination, J. A. M. A. **135:***729 (Nov. 15) 1947.* This letter from THE JOURNAL's Paris correspondent summarizes briefly the views of French doctors, lawyers and theologians concerning artificial insemination.

Queries and Minor Notes, J. A. M. A. **110:***1857 (May 28) 1938.* The answer to a query concerning the practicability of artificial insemination calls attention to possible social, legal and certain physiologic dangers which should be considered by the physician contemplating this operation.

Seashore, R. T.: Artificial Impregnation, Minnesota Medicine, pp. 641-644, Sept. 1938. (Minnesota Medicine, 2642 University Ave., St. Paul 4, Minnesota.) The author in presenting a case discusses the legal aspects of this operation as it actually occurred to him, a physician, and his attorney. The article contains a form of consent, outlines procedure for its use and makes a recommendation as to custody of the consent forms.

Guttmacher, A. F., Role of Artificial Insemination in the Treatment of Sterility, J. A. M. A. **120:***442 (Oct. 10) 1942.* Dr. Guttmacher in discussing the social aspects of artificial insemination, having discussed the medical aspects, sets forth four rules described as common sense rules to be followed by the doctor in any case of contemplated artificial insemination.

Haman, J. O.: Artificial Insemination, California Medicine, pp. 353-357, May, 1948. (California Medical Association, 450 Sutter St., San Francisco 8, California.) The author presents a form of consent the use of which by the couple is advocated chiefly as protection for the physician. The author calls attention to the fact that the type of legislation which may be enacted will depend upon the care or lack of care by physicians in performing this operation, concluding that lack of care and integrity by physicians will arouse public opinion and engender legislation banning this practice.

Forbes, R.: The Medico-Legal Aspects of Artificial Insemination, The Medico-Legal and Criminological Review, **12:***138 (July-Sept.) 1944.* (The Medical Defense Union, 49 Bedford Square, London, W.C.I., England.) The principal part of this article, read by Dr. Forbes, Secretary of the Medical Defense Union of England, before the Medico-Legal and Criminological Society, develops the history and medical aspects and the legal pitfalls of artificial insemination. The reported comments of the doctors and lawyers of the audience offer varied observations as to the practice and some pertinent suggestions relative to legal problems involved.

Comment (Author not named) Artificial Insemination: A Parvenu Intrudes on Ancient Law, The Yale Law Journal, **48:***457 (Feb.) 1949.* (Yale Law Journal Co., 127 Wall St., New Haven, Conn.) This article develops the thesis that because the operation of heterologous insemination, AID, was unknown and unthought of while laws developed legislatively and judicially the legal problems which may obtain by reason of the operation cannot be answered by reference to the law as it stands. The article concludes that legislative decision is the only ultimate solution to the legal questions involved and discusses briefly principles, legal and social, which in the writer's opinion should be considered to achieve sound legislation.

The Report of a Commission Appointed by His Grace The Archbishop of Canterbury, Artificial Human Insemination, (Feb.) 1948. (Printed by The Talbot Press, SPCK, Saffron Walden, Essex, England.)

Artificial Insemination—Illegitimacy (Editorial), J. A. M. A. **112:***1832 (May 6) 1939.* This editorial suggests that a child born after an artificial insemination, the donor being a person other than the husband of the woman inseminated, must be considered as illegitimate and adoption proceedings are advocated.

J. G. P.: Artificial Insemination v. Adoption, Virginia Law Review, October, 1948. (Virginia Law Review Association, Charlottesville, Virginia.) The author expresses his opinion that heterologous artificial insemination is contrary to law and suggests that couples who are incapable of having children resort to adoption procedures rather than this operation.

Artificial Insemination (Editorial), The Journal of the Indiana State Medical Association, July, 1950. (1017 Hume Mansur Bldg., Indianapolis 4.) This editorial expresses doubt that the procedure violates any criminal law and suggests that when consent to the operation is obtained from the husband authorizing the insemination of his wife with the semen of a donor, the child, if one results, is legitimate.

Russel, M.: A Plea for Standardization of Donors, J. A. M. A. **144:***461 (Oct. 7) 1950.* The author states that a doctor in performing this procedure should carefully investigate the background of the donor as well as examine him physically and lists the qualifications which, in his opinion, should be sought in donors.

Artificial Insemination (Abstracts of Papers), The Medico-Legal Journal, Part One, 1950. (The Medico-Legal Society, 125, High Holborn, London, W.C.I.) Papers presented to the Manchester branch of the Society and discussion following their presentation are abstracted. Legitimacy of issue, the legality of the operation, and the question of whether the procedure is adultery were ably considered.

Problems of Artificial Insemination (Editorial), New York State Journal of Medicine, March 15, 1948. (Medical Society of the State of New York, 292 Madison Avenue, New York 17, New York.) This editorial discusses the *Strnad* case as it points up problems connected with artificial insemination.

Artificial Insemination (Editorial), British Medical Journal, May 3, 1947. (British Medical Association, Tavistock Square, London, W.C.I.) The view is expressed that heterologous artificial insemination may be adulterous and the resulting child illegitimate. It is suggested that the doctor who engages in this practice, though not guilty of a criminal offense, stands on insecure ground and close to dangerous pitfalls.

Regan, L. J.: Doctor and Patient and the Law, ed. 2, C. V. Mosby Company, St. Louis, 1949.

Schatkin, S. B.: Disputed Paternity Proceedings, ed. 2, Matthew Bender Company, New York City, 1947.

Dr. Regan's book considers the several aspects of artificial insemination. He includes a suggested form of consent to be used by the parties who undergo this procedure. In Mr. Schatkin's book the question of legitimacy is discussed.

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FORM OF CONSENT

The following form has been suggested for use in artificial insemination cases.[1]

CONSENT TO ARTIFICIAL INSEMINATION

WHEREAS, We, the undersigned.....and....., are husband and wife, having been married in the City of....., County of ....., State of....., and

WHEREAS, this marriage has to the present time been childless, and

WHEREAS, we are desirous of having a child and have been informed that.....is incapable of procreation;

NOW, THEREFORE, we and each of us do hereby request and authorize Dr.....to select a donor, who in his sole discretion and judgment will meet the following qualifications:

We and each of us further request and authorize the said Dr..... to obtain from said donor sperm necessary to inseminate the said ....., and to thereupon artificially inseminate her with said sperm in the usual and customary manner, and to do such acts in furtherance thereof as may seem necessary and advisable in the sole discretion of Dr.....

We and each of us understand that said Dr.....does not warrant or guarantee the qualifications of said donor, and that in determining whether the said donor meets the aforesaid qualifications the said Dr.....shall be required to make only such investigation of and concerning such donor as shall in the sole discretion of said Dr..... seem reasonably necessary.

We and each of us further agree that we shall not now, nor at any future time require nor expect said Dr.....to obtain or divulge to us the name of said donor, nor any other information concerning said donor's race, nationality, characteristics, qualities, or any other information whatsoever concerning said donor.

We further agree that following the said insemination the said Dr.....shall destroy all information and records which he may have as to the identity of said donor, it being the intention of all parties that the identity of said donor shall be and forever remain anonymous.

We and each of us further covenant and agree to forever refrain from instituting, pressing or in any way aiding any claim, demand, action or cause of action for damages, costs, loss of services, expense or compensation for or on account of or hereafter arising out of the premises hereinabove set forth.

We and each of us further promise and agree to indemnify and save harmless the said Dr.....from any loss and/or expenses incurred by him in connection with the defense or payment of any claim or action arising out of the aforesaid premises or agreements herein contained.

This agreement shall be binding upon ourselves, and each of us, our assigns, heirs, executors and administrators.

Dated this.....day of....., 19....

.....
(Husband)

.....
(Wife)

WITNESSES:

.....

.....

Relying upon the authorization and agreements above set forth, I hereby agree to obtain a donor and to artificially inseminate the said.....

DATED this.....day of....., 19....

.....

CONCLUSION

Distinct difference of opinion exists concerning the legality of heterologous artificial insemination and the legitimacy of children resulting therefrom. Reconciliation of these opposite points of view is difficult. The extent of a physician's responsibility in selecting a donor and performing this operation, if it is performed, is uncertain.

A physician, before undertaking the procedure, will act wisely if he advises the husband and wife as to the legal implications or uncertainties of the operation as it affects them as husband and wife and as it may affect the child's status at law.

1. Regan, L. J.: Doctor and Patient and the Law, St. Louis, C. V. Mosby Company, 1949.

COUNCIL ON PHARMACY AND CHEMISTRY

REPORT TO THE COUNCIL

The Council has authorized publication of the following report to the Council submitted by Arthur M. Walker, M.D., Secretary of the Veterans Administration Committee on Streptomycin.

R. T. STORMONT, M.D., *Secretary.*

CHEMOTHERAPY OF TUBERCULOSIS IN MAN

PRESENT STATUS

This paper is essentially a progress report of the clinical study initiated by the Veterans Administration, Army, and Navy in June, 1946, and is a continuation of three reports published previously in these columns.[1] The most recent of the three described the situation as it existed at the time of the Eighth Streptomycin Conference in November, 1949. The present article carries the account forward to the Tenth Conference on the Chemotherapy of Tuberculosis in January, 1951. During this interval, the number of cases reported to the study has increased from 7,000 to approximately 10,000; the goal of recording data from individual cases on punch cards has, in some measure, been achieved, thus increasing the reliability of the data; certain disadvantages of streptomycin have been partially overcome, and the effects of some new chemotherapeutic agents have been explored in a preliminary fashion. Hence, this report. Although it concerns itself primarily with the results of a single cooperative study, the conclusions this report presents are believed to be compatible with those of the majority of the other investigators in the field.

From the outset it has been unpleasantly clear that streptomycin does not "cure" tuberculosis.[2] Since the disease occurs in many forms and is chronic by nature, perhaps this was not to be expected. Although some patients with miliary or meningeal tuberculosis are alive who otherwise would be dead, and a large number of muco-cutaneous lesions have healed [1b] which, otherwise, scarcely would have done so, the central problem, a cure for pulmonary tuberculosis, remains. The aim of the investigation has been to extract the greatest possible benefit from the drugs at hand by overcoming their disadvantages and by employing them in combination with bed rest and appropriate surgical procedures. If the infrequency with which streptomycin cures tuberculosis is disregarded for the moment, two disadvantages remain: the drug's toxicity, and the frequency with which strains of tubercle bacilli resistant to it appear during treatment. Since the two difficulties apply to the reduction product, dihydrostreptomycin, as well as to the parent drug, both antibiotics will be considered simultaneously in these respects.

TOXICITY

The obvious way to diminish or avoid the toxic effects of a drug is to decrease its dosage. To this truism, however, must be added another: if the diminution in toxicity involves a concomitant reduction in therapeutic efficacy, the investigator must weigh the advantages of the one result against the disadvantages of the other. Fortunately, this dilemma can be avoided for the most part in the present instance.

Remarks on the toxicity of the two antibiotics under discussion can be confined, for all practical purposes, to their effect

Prepared by the Veterans Administration, Washington, D. C., at the request of the Tenth Veterans Administration-Army-Navy Conference on the Chemotherapy of Tuberculosis, Atlanta, Ga., Jan. 25-28, 1951.

1. Reports to the Council on Pharmacy and Chemistry: (*a*) The Effects of Streptomycin on Tuberculosis in Man, J. A. M. A. **135**: 634 (Nov. 8) 1947. (*b*) Streptomycin in the Treatment of Tuberculosis: Current Status, ibid. **138**: 584 (Oct. 23) 1948. (*c*) Current Status of the Chemotherapy of Tuberculosis in Man; A Summary Report, ibid. **142**: 650 (March 4) 1950.

2. Hinshaw, H. C., and Feldman, W. H.: Streptomycin in Treatment of Clinical Tuberculosis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **20**: 313, 1945.

upon the eighth cranial nerve. Signs of renal irritation, skin eruptions, and fever occur occasionally in patients, and allergic phenomena may develop in nurses who handle the drugs, but both drugs are relatively non-toxic except for their singular action on the vestibular and auditory apparatus. Vertigo, accompanied usually by ataxia and by diminished response to caloric stimulation, is the commonest toxic manifestation of streptomycin therapy. It occurred, sometimes to an incapacitating extent, in 80% of 671 patients receiving 2 gm. of the drug daily for 120 days.[1b] Cutting down duration of treatment to 60 days reduced the incidence to 63%, but a reduction in dosage was even more successful. Vertigo occurred in only 8% of 1,006 patients receiving a single daily injection of 1 gm. per day, in 5.8% of 137 patients receiving 0.5 gm. per day, and in 3.4% of 383 patients receiving 1gm. twice a week (Table 13 [3a]). Each of these three regimens was continued for 120 days and in only two instances the vertigo was described as "severe" or "incapacitating." Further—a point which will be discussed subsequently—these reductions in dosage were accomplished without any detectible loss of therapeutic efficacy. This statement is made with reservations only for the 0.5 gm. per day regimen.

A second method of decreasing the incidence of vertigo, which began in the fall of 1948, involves substituting dihydrostreptomycin for streptomycin. The advantage is very much in favor of dihydrostreptomycin at a dosage level of 2 gm. per day [1b, c]; but, since the study had already reached the conclusion that the daily dose of streptomycin need not exceed 1 gm. per day, the advantage is more apparent than real. At the lower dosage level, the difference is relatively slight (8% as opposed to 3%).[3b] For this reason and because, after a study of 800 cases, the advantage in therapeutic efficacy seemed to favor use of streptomycin, the use of dihydrostreptomycin has been discontinued in the study. Another factor which led to this decision was the discovery that dihydrostreptomycin was more prone to produce deafness, which can occur even at a dosage of 1 gm. per day if treatment be continued for longer than four months.[4] According to Romansky [3b] and Glorig,[3c] a loss of hearing exceeding 30 decibels occurred in 40% of 83 patients receiving 2 gm. per day for less than four months. This toxic reaction, as amazing in its specificity as the vertigo produced by streptomycin, is possessed to an even greater degree by hydroxystreptomycin (Hawkins [3c]).

Some progress has been made, then, in controlling the toxic effects of streptomycin on the eighth cranial nerve by diminishing the amount and frequency of its administration, the most satisfactory regimen being 1 gm. twice a week.

DRUG RESISTANCE

The second disadvantage of streptomycin therapy is the frequency with which cultures of tubercle bacilli, obtained from patients, become inured to the drug and are able to grow in considerable concentrations of it. It has been natural and reasonable to interpret this situation as indicating that all the tubercle bacilli in the patient's lungs (or eleswhere) are similarly resistant and that further treatment with streptomycin is useless. This does not appear to be entirely true in man when the bacilli are resistant to 10 γ per cubic centimeter or even when they are partially resistant (i. e., show less growth than in the control tube) to 100 γ per cubic centimeter (Table 1c [3c]). It is true, however, in man when the bacilli are completely resistant to 100 γ per cubic centimeter or more and in guinea pigs at concentrations much less than this. For the purposes of our present discussion, then, it may be accepted that the emergence of resistance is a disadvantage to streptomycin therapy.

With the regimen first employed in this study, a daily dosage of 2 gm. of streptomycin, 82% of all positive cultures were found resistant to 10 γ or more per cubic centimeter after 120 days of therapy. As long as the duration was maintained at 120 days, this incidence could not be decreased by reducing the daily dosage to 1 or 0.5 gm.[1b] The obvious expedient of decreasing the duration of treatment was therefore explored in a series of 6 regimens (employing streptomycin or dihydrostreptomycin) extending over 90, 60, and 42 days. This last regimen reduced the incidence of resistance among positive cultures to approximately 45%,[1c] but this incidence is still uncomfortably high. Also, the 42-day regimen was clearly inferior in therapeutic efficacy as gauged by x-ray improvement and sputum conversion. Reducing duration of treatment did not provide a satisfactory solution to the difficulty.

Therefore, two other procedures were investigated by the study: the concomitant use of *p*-aminosalicylic acid (PAS) with streptomycin, and the use of 1 gm. of streptomycin twice a week rather than daily, a regimen first used by Fitzsimons General Hospital. The study has not found *p*-aminosalicylic acid, given alone in a daily oral dosage of 12 gm., to be as effective for treating pulmonary tuberculosis as it has been reported by Swedish investigators, because "moderate" or "marked" radiologic improvement occurred in 48% of 739 patients receiving streptomycin and in only 17% of 247 patients receiving *p*-aminosalicylic acid.[3c] In the figures just quoted, it could be argued properly that the scales had been weighted against *p*-aminosalicylic acid, since the patients receiving it had already received a course of streptomycin and the necessity for further chemotherapy may well have indicated the presence of a more malignant type of disease. However, there can be no doubt of the favorable effect exerted against the development of resistance to streptomycin by concomitant therapy with *p*-aminosalicylic acid. Thus, of 224 patients treated with the combined regimen, only 31% (instead of 82% treated with streptomycin alone) of those cultures which continued to be positive after 120 days of therapy were resistant to 10 γ or more per cubic centimeter of streptomycin.[3c] The second procedure, that of decreasing the frequency of injections to twice a week, also met with some measure of success. Resistant bacilli appeared more slowly and, after 120 days of therapy, 67% (rather than 82%) of 118 positive cultures were resistant by the same criteria. (Tempel et al [3c]).

Since both of these procedures seemed promising independently, the obvious indication was to use them both in "combined, intermittent therapy" (i. e., 1 gm. of streptomycin twice weekly plus 12 gm. of *p*-aminosalicylic acid daily, given concurrently). Under these circumstances, the incidence of resistance among positive cultures decreased to 17% after 120 days of therapy (Table 12 [3c]).

Several matters of some interest in connection with resistance may bear brief mention:

1. Although resistance to *p*-aminosalicylic acid develops, its incidence does not usually exceed 10% after 120 days of combined streptomycin and *p*-aminosalicylic acid therapy (Table 12 [3c]). When *p*-aminosalicylic acid is given alone (i. e., in the absence of streptomycin), the incidence of resistance is about 45%.

2. No attempt has yet been made by members of the study to determine the minimum effective dose of *p*-aminosalicylic acid, but Fitzsimons General Hospital has presented evidence favoring its daily rather than biweekly administration. Patients have objected strenuously to attempts to increase the daily oral dosage to 18 or 24 gm.[3c]

3. Since tubercle bacilli have been rendered resistant to streptomycin in so many patients and since this resistance is relatively permanent, it is surprising that so few other patients appear to have been infected by them. This matter does not seem to pose the serious public health problem envisaged earlier.

4. An increasing number of cases are being reported in which, some months or even years after cessation of streptomycin therapy and development of resistant bacilli, sensitive cultures have been obtained. This no longer seems likely to be a laboratory error but rather an expression of the heterogeneity of the bacillary population with regard to streptomycin.

In this matter of resistance, then, considerable progress has been made, most notably by using *p*-aminosalicylic acid in combination with streptomycin, and also by injecting the latter drug less frequently. Before these factors were introduced, incidence of resistance was about 82% to 10 γ per cubic centi-

3. (*a*) Minutes of the Eighth Streptomycin Conference, Nov. 10-13, 1949; (*b*) Transactions of the Ninth Streptomycin Conference, April 18-21, 1950; (*c*) Transactions of the Tenth Conference on the Chemotherapy of Tuberculosis, Jan. 25-28, 1951, published by the Veterans Administration.

4. O'Connor, J. B.; Christie, F. J., and Howlett, K. S., Jr.: Neurotoxicity of Dihydrostreptomycin: Effects of Longer-Term Therapy, Am. Rev. Tuberc. **63**: 312, 1951. D'Esopo.[3b, c]

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meter after 120 days of therapy; it is now less than 20%. The incidence of resistance to 100 γ or more per cubic centimeter has been decreased from 62% to 5% by the same procedures.

PULMONARY TUBERCULOSIS

The advances made in overcoming the factors of toxicity of, and bacterial resistance to, streptomycin would have been useless if accomplished at the expense of therapeutic efficacy. Although passing reference to this point has already been made, it is of such outstanding importance that supporting data is supplied in Table 1. For simplicity in presentation, the criteria have been confined to radiologic change and sputum conversion (by culture), a simplification justified by past experience. The patients in regimen 1 (2 gm. streptomycin daily) were treated in 1946 and 1947, whereas those in regimens 2 and 3 were treated in 1949 and 1950; and *p*-aminosalicylic acid is absent from regimen 1 and present in the other regimens. However, alternate patients were assigned to regimens 2 and 3 on the basis of hospital registration numbers and background factors (e. g., race, age, extent and trend of disease) in each group were carefully analyzed and proved satisfactorily similar. The encouraging difference in incidence of sputum conversion is presumably due to the concomitant collapse therapy permitted with the last two regimens. At any rate, there can be no doubt that the regimens in present use (2 and 3) have maintained the therapeutic efficacy of the earlier one which contained larger doses of streptomycin and did not include *p*-aminosalicylic acid.

TABLE 1.—*Comparison of Therapeutic Efficacy of Three Regimens in Pulmonary Tuberculosis (at End of Therapy)*

Results	(1) 2.0 Gm. Streptomycin Daily, 120 Days		(2) 1.0 Gm. Streptomycin Daily + 12.0 Gm. PAS Daily, 120 Days		(3) 1.0 Gm. Streptomycin Semiweekly + 12.0 Gm. PAS Daily, 120 Days	
	No. Cases	Percentage	No. Cases	Percentage	No. Cases	Percentage
Radiologic improvement						
Moderate or marked..	248	66	209	48	139	46
Slight	64	17	131	30	94	31
All degrees	312	83	340	78	233	77
Total cases observed..	375	100	436	100	303	100
	No. Cases Observed	Percentage Converted	No. Cases Observed	Percentage Converted	No. Cases Observed	Percentage Converted
Sputum conversion (culture)	120	32	316	59	209	56

The abbreviated data of Table 1 are all obtained at the 120-day point after the beginning of therapy. No mention has been made of follow-up or of the relapses which occur in pulmonary tuberculosis. Such information is beginning to become available. Commander Canada and his collaborators have published a three-year follow-up of 202 cases in which the earliest regimen,[5] 2 gm. of streptomycin daily for 120 days, was used. They reported that 28% of the patients were dead, arrest or apparent arrest of disease had occurred in 40%, approximately one-third of the survivors were gainfully employed, and one-half were able to be up and about for nine hours or more per day. The incidence of sputum conversion had increased to 50% after completion of therapy, and one-half of the survivors who had exhibited vestibular disturbances during therapy continued to show some residuals, although in only 6% was it of sufficient degree to interfere with a gainful occupation. In the absence of a comparable series of patients not treated with streptomycin, it is difficult to know precisely how these figures should be regarded; but the fact that the disease was progressive in 84% (and improving in only 3%) at the time treatment was started, carries considerable weight in the judgment of the study. It should be remarked that collapse procedures were used in approximately two-thirds of the cases following chemotherapy.

Follow-up data describing the effects of eight regimens on 813 cases during the preceding year (discussion of Table 1B [3c]) were presented before the conference of January, 1951. Analysis was more competent than in previous series because background material was available and seemed satisfactorily comparable in each group. Regimens enduring for 120 days appeared superior to those of 90 days. On the other hand, little or no difference in therapeutic efficacy could be demonstrated by the substitution of interrupted (twice weekly) for daily therapy, or by substituting dihydrostreptomycin for streptomycin in equivalent (1 gm. daily) dosage.

The primary concern of the Veterans Administration-Army-Navy study has been the comparative examination of regimens in an attempt to "bracket the target" and to gain maximum therapeutic efficacy with minimum toxic manifestations and bacterial resistance. The investigators in the study were so thoroughly convinced that *p*-aminosalicylic acid should always be given concomitantly with streptomycin that the latter drug has not been used alone (except in special circumstances) since the fall of 1949. The decision is not based on any increased effectiveness of the combined therapy during regimens of 120 days or less which, indeed, has not been detectable, but on delay in the development of resistant bacilli and, presumably, consequent prolongation of the effective period of streptomycin. This delay has raised the interesting and logical possibility of prolonging treatment for 8 or 12 months, or even more. These prolonged regimens, first used by the Veterans Administration Hospital at Sunmount, N. Y., have been the chief concern of the study since April, 1950. The initial results of this project have been very promising. One of the most striking effects has been the difficulty in obtaining positive sputum cultures (i. e., an increased incidence of sputum conversion) as long as the combined therapy was continued (Table 1A [3c]). It is, of course, too early to make any precise statements on these matters, but it is the opinion of the study group that the use of prolonged regimens should be seriously considered.

EXTRAPULMONARY TUBERCULOSIS

The indications for the use and success of chemotherapy in extrapulmonary tuberculosis have not changed recognizably in the past year. Therefore, they deserve no place in a capsule summary. With two exceptions to be mentioned, the study group no longer collects data on current experience in these fields and has abolished its protocols. The comments previously made [1b] are believed still applicable if combined with the suggested adjustments in dosage.

1. *Miliary and Meningeal Tuberculosis.*—Although mortality from these infections is highest in the first year after their diagnosis, an appreciable number of deaths from relapses following meningitis and, usually, from the development of complicating meningitis following miliary tuberculosis occurs during the second year. An evaluation of therapy is therefore scarcely justified before expiration of a two-year period. This was pointed out by Bunn [6] in a two-year follow-up of the first 100 patients treated in this study. At the time of his presentation, the survival rate was 58% in 19 cases of miliary tuberculosis unaccompanied by meningitis and 20% in 43 cases of tuberculosis meningitis. Both groups are exceedingly small, and the results are inferior to many series reported from abroad and by Lincoln,[7] for example, in this country. In some series the discrepancy may be due to an inadequate follow-up and in others to the fact that the patients were mostly, or entirely, children. But there is no agreement on this matter and members of the conferences have never felt sufficiently sure of themselves to formulate any exact protocol for the treatment of these types of tuberculosis. Consequently, the investigators have used a wide variety of regimens, making statistical analysis difficult. Little has been learned, although during the past year or two *p*-aminosalicylic acid has been used in combination with streptomycin or dihydrostreptomycin with some improvement in immediate results

5. Canada, R. O.; Allison, S. T.; D'Esopo, N. D.; Dunner, E.; Moyer, R. E.; Shamaskin, A.; Tempel, C. W., and Charter, W. V.: Three-Year Follow-Up Study on 202 Cases of Pulmonary Tuberculosis Treated with Streptomycin, Am. Rev. Tuberc. **62:** 563, 1950.

6. Bunn, P. A.: Two-Year Follow-Up Report of Patients with Miliary and Meningeal Tuberculosis Treated with Streptomycin, Am. J. M. Sc. **219:** 127, 1950.

7. Lincoln, E. M., and Kirmse, T. W.: Streptomycin-Promizole Therapy of Miliary and Meningeal Tuberculosis in Children, Am. Rev. Tuberc. **61:** 159, 1950.

(Table 2). The data in Table 2 cover only one year after the start of treatment. After a year's treatment the advantage of combined therapy appears to be much less (Table 9[3c]), although the number of cases is insufficient to warrant a definite statement on this point. However, the conference group of January, 1951, felt justified in making combined therapy obligatory in future treatment, even to the extent of advising parenteral administration of *p*-aminosalicylic acid if the drug could not be given by mouth.

The intrathecal use of tuberculin in the treatment of meningitis, suggested and practiced by Smith and Cairns of Oxford, was discussed at some length in the conference.[3c] The most recent account of this procedure was presented before the National Tuberculosis Association by Smith in April, 1951. Although it was agreed that the results were striking, members of the conference felt that the procedure was too hazardous to warrant their making any recommendation at this time.

2. *Genitourinary Tuberculosis.*—The only data in this field which it has seemed necessary to collect for recent conferences are those dealing with bacteriologic follow-up. One hundred and twenty-three patients in the series now have been observed for more than one year since the completion of a first course of chemotherapy and 100 for more than two years. In an attempt

TABLE 2.—*Mortality in Miliary and Meningeal Tuberculosis**

	Streptomycin or Dihydrostreptomycin			Streptomycin or Dihydrostreptomycin and *p*-aminosalicylic Acid		
	No. of Cases Observed	Alive, %	Dead, %	No. of Cases Observed	Alive, %	Dead, %
Miliary only						
At start of therapy.....	59	100	0	43	100	0
At end of 6 mo.....	55	65	35	28	79	21
At end of 12 mo.....	48	54	46	20	65	35
At end of 24 mo.....	37	27	73	..†	..	..
Meningitis only						
At start of therapy.....	93	100	0	44	100	0
At end of 6 mo.....	90	42	58	39	62	38
At end of 12 mo.....	86	21	79	28	40	60
At end of 24 mo.....	80	11	89	..	..	..
Miliary and meningitis						
At start of therapy.....	38	100	0	15	100	0
At end of 6 mo.....	37	41	59	12	67	33
At end of 12 mo.....	36	14	86	11	55	45
At end of 24 mo.....	36	8	92	..	..	..
Miliary followed by meningitis						
At start of therapy.....	30	100	0	19	100	0
At end of 6 mo.....	30	40	60	17	71	29
At end of 12 mo.....	30	20	80	17	24	76
At end of 24 mo.....	29	0	100	..	..	..

* Based on data presented to the Tenth Conference, January, 1951, Table 9.

† Where no figures are given, an insufficient number of cases was observed.

to clarify interpretation of the data, the lesions were classified under "renal only," "genital only," and "combined renal and genital." Data on five regimens were presented to the conference of January, 1951 (Table 8[3c]). The outstanding finding (by culture or guinea pig) was that the conversion of urine from positive to negative had withstood the passing of time surprisingly well. In the renal lesions there was a drop from 53% (immediately after treatment) to 47% (more than two years later), in genital lesions from 78% to 70%, and in combined lesions from 50% to 33%. The 2 gm. of streptomycin daily seemed slightly more effective than 1 gm. daily, and the 42-day appeared definitely less effective than the 120-day regimen. Data on the combined regimens were insufficient to determine whether any advantage had been gained by the addition of *p*-aminosalicylic acid. The conference members decided, as they had for pulmonary tuberculosis, to extend the duration of treatment beyond 120 days and to explore the effect of the interrupted (twice a week), combined streptomycin and *p*-aminosalicylic acid schedule.

PROTECTION IN THORACIC SURGERY

Early in the course of this study, the protective effect of streptomycin against postoperative extensions of infection was studied by use in alternate cases of thoracoplasty for seven days prior, and 14 days subsequent, to operation. This study was discontinued in April, 1948, not because the effect of streptomycin in decreasing the incidence of complications did not seem clear but because their incidence in untreated patients was too low to justify the procedure.[1b] Use of streptomycin was continued, however, in all patients subjected to pulmonary excisions and decortications. At first the procedure seemed highly satisfactory,[1b] but subsequently, despite its continuance, the incidence of complications increased from twofold to fourfold.[1c] The indications for resectional surgery have unquestionably been broadened during the past three years to include many cases that would have been regarded as impossibly "bad risks" before the advent of chemotherapy and improved surgical techniques. In this extension of surgery may lie the explanation for the increase in complications. But the question also arose as to whether deterioration in results was due to streptomycin's being administered to patients who had received a previous course of the drug and whose bacilli were therefore resistant to it. Data presented to the conference of January, 1951 (Table 11[3c]), and summarized in Table 3 of this paper, indicate that this is only partially true. Thus, although results were manifestly inferior in patients with bacilli resistant to streptomycin at the time of prophylactic chemotherapy, they were somewhat inferior in those with bacilli still sensitive to concentrations of less than 10 γ per cubic centimeter despite a previous course of the drug. Two negative statements, neither of them satisfying, are warranted: 1. The increased incidence of postoperative complications in this study since 1948 is not wholly due to previous chemotherapy. 2. Insofar as this increase in complications is associated with previous chemotherapy, it is not wholly due to the presence of resistant bacilli prior to surgery, although it may well be that the bacilli of patients treated prior to surgery become resistant more rapidly than do those from patients who received no previous chemotherapy.

THERAPY WITH SUBSTANCES OTHER THAN STREPTOMYCIN OR DIHYDROSTREPTOMYCIN

Late in 1948, it was stated that it "would be strange if the first antibiotic that proved to be bacteriostatic in the treatment of human tuberculosis were to be the best."[8] However, this is precisely what has happened thus far. There is no lack of rivals, but, according to the results of the study, streptomycin still leads the field by the widest of margins. Nonetheless, other antibiotics deserve some brief mention.

1. *Other Antibiotics.*—Neomycin, viomycin, and mycomycin are of peculiar interest, because their in vitro activity is specific for acid-fast microorganisms and because they are effective against tubercle bacilli that have become resistant to streptomycin. Neomycin has had some clinical trial and, in the purest preparations available, has proved not only to be a renal irritant but also to be highly toxic to the cochlear branch of the eighth cranial nerve. In two small series reported to the conference of January, 1951, 10 of 18 patients were said to have become totally deaf and a similar experience was reported in a larger series of 43 cases.[3c] Viomycin has been employed in 49 cases of pulmonary tuberculosis in seven clinics (five of which are outside the study).[9] A preliminary report to the conference of January, 1951, indicated viomycin to be less effective and more toxic than streptomycin.[3c] Since one of its toxic effects is on the eighth nerve, it seems unlikely that it will be useful as adjunctive therapy with streptomycin. Mycomycin is still in the

8. Walker, A. M.; Hinshaw, H. C., and Barnwell, J. B.: Streptomycin in Treatment of Tuberculosis in Man, in Waksman, S. A.: Streptomycin: Its Nature and Application, Baltimore, The Williams & Wilkins Company, 1949, chap. 18.

9. Finlay, A. C., and others: Viomycin, a New Antibiotic Active Against Mycobacteria, Am. Rev. Tuberc. **63**: 1, 1951. Bartz, Q. R., and others: Viomycin, a New Tuberculostatic Antibiotic, ibid. **63**: 4, 1951. Ehrlich, J., and others: Antimicrobial Activity of Streptomyces Floridae and of Viomycin, ibid. **63**: 7, 1951. Hobby, G. L., and others: Activity of Viomycin Against Microorganisms in Vitro and in Vivo, ibid. **63**: 17, 1951. Youmans, G. P., and Youmans, A. S.: Effect of Viomycin in Vitro and in Vivo on Mycobacterium Tuberculosis, ibid. **63**: 25, 1951. Steenken, W., Jr., and Wolinskey, E.: Viomycin in Experimental Tuberculosis, ibid. **63**: 30, 1951. Karlson, A. G., and Gainer, J. H.: Effect of Viomycin in Tuberculosis of Guinea Pigs, Including in Vitro Effects Against Tubercle Bacilli Resistant to Certain Drugs, ibid. **63**: 36, 1951. P'an, S. Y., and others: Viomycin: Acute and Chronic Toxicity in Experimental Animals, ibid. **63**: 44, 1951. Werner, C. A., and others: Toxicity of Viomycin in Humans, ibid. **63**: 49, 1951.

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laboratory development stage, the chief difficulty encountered being concerned with its stability at room temperature.[3b, c] Although progress is being made, it would still be almost necessary to have the patient inside a deep-freeze with the drug if a clinical trial were to be made.

Unlike the three antibiotics just mentioned, aureomycin and terramycin have relatively little tuberculostatic activity in vitro, but, because they are somewhat effective under these circumstances and relatively nontoxic, clinical trials appeared justified. (These trials, like numerous others, including one calling for the single weekly injection of 2 gm. of streptomycin initiated by the Navy, are referred to as pilot studies and are regarded as one of the most useful functions of the study. Hospitals are asked to participate, and thus it becomes possible to collect preliminary data on a considerable number of matters for the guidance of future conferences.) For aureomycin, only one hospital was involved and only 10 patients were treated, but the selection of patients was such that it seemed permissible to conclude that the effects were no more beneficial than could have been expected from bed rest alone.[3a] To the conference of January, 1951, six hospitals reported on a pilot study with terramycin. The study had been in progress for approximately six months, and 62 patients had been treated. There was some disagreement concerning results, as five hospitals were thoroughly unimpressed whereas one (Fitzsimons) felt that a beneficial effect had been observed and, furthermore, that the emergence of resistance to streptomycin appeared to be suppressed or delayed when the two drugs were given concurrently.[3c]

2. *Hormones.* — A modest symposium on corticotrophin (ACTH) and cortisone was held during the conference of January, 1951.[3c] The rabbit was added to the previous three laboratory animals (mouse,[10] guinea pig,[11] rat [12]) in which definitely harmful effects were proved to have been exerted by these hormones in the presence of experimental tuberculosis. The lesions were more extensive, more numerous, and death occurred earlier than in untreated control animals. In the course of general discussion, approximately 20 cases of clinical tuberculosis were reported in which, after the anticipated initial symptomatic improvement, the end results of treatment were unfavorable. Tuberculosis seems to be another of the "infectious diseases in which these hormones provide a physiological tool rather than a therapeutic weapon" (Finland [3c]). Although the conference group does not seek to advise the medical profession, it felt justified in endorsing the statement of the National Tuberculosis Association that these hormones "should not be used in patients with active tuberculosis and that they be used with extreme caution in human beings with possibly latent tuberculous infection until further investigative work has shown that such administration may be safe." [13]

3. *Miscellaneous.*—Amithiozone (tibione®) is the only thiosemicarbazone with which the study group has had experience, and this experience has not been altogether satisfactory. It was employed at a daily dosage of 0.2 gm. in 226 cases of pulmonary tuberculosis of which approximately one-half were resistant to streptomycin. Although some patients, including those resistant to streptomycin, showed considerable radiologic improvement after four months' therapy, the incidence was much less than that obtained with other regimens (Tables 1C and D [3c]). Also, amithiozone's toxicity greatly exceeded either that of streptomycin or *p*-aminosalicylic acid, so that it was necessary to stop treatment in one-third of the cases. The chief toxic manifestations of amithiozone are liver damage (proved by biopsy) and blood dyscrasias, particularly a fall in hemoglobin. Although both of these lesions seem to be reversible, their existence leaves doubt as to the wisdom of amithiozone therapy. The study is to be continued on a smaller basis, with a daily dosage of 0.1 gm., in the hope of diminishing or avoiding these toxic effects.

Cepharanthin is an alkaloid used widely in Japan during recent years for treating tuberculosis and leprosy. Although the reports are more enthusiastic than critical, laboratory work in this country has indicated that it does not warrant a clinical trial.[14]

p-Aminosalicylic acid, already discussed at as great a length as this type of presentation permits, is mentioned again to cite the fact that pilot studies intended to minimize its untoward effects on the gastrointestinal tract by the use of a variety of capsules and granules have been unsuccessful. Four grams is being given three times daily in solution as the sodium salt with meals without too much difficulty.

Benemid does not affect tuberculosis. It is being employed in a pilot study to determine its effect on the serum concentrations of *p*-aminosalicylic acid.

TABLE 3.—*Protection in Pulmonary Surgery**

Type of Surgery	No. of Cases	Sputum, Culture, or Guinea Pig: Converted %	Not Converted %	Unknown %	Postoperative Complications: Spread %	Fistula %	Empyema %	Wound Infection %	Operative Deaths %
Lobectomy									
No previous streptomycin	337	72	16	12	8.1	3.8	2.0	2.6	1.8
Previous streptomycin									
Resistant	47	34	53	13	20.8	29.2	18.8	6.3	2.1
Sensitive	133	58	28	14	10.9	8.0	5.8	2.9	1.5
Resistance unknown	141	70	13	17	8.2	6.1	2.0	3.4	2.1
Pneumonectomy									
No previous therapy	150	75	14	11	10.0	8.7	9.3	6.7	10.0
Previous therapy									
Resistant	50	50	44	6	24.0	24.0	28.0	24.0	16.0
Sensitive	53	60	21	19	12.9	16.7	22.2	13.0	9.4
Resistance unknown	52	54	33	13	13.2	17.0	18.9	9.5	9.6
Decortication									
No previous therapy	113	56	27	17	2.6	7.9	7.0	4.4	0.9
Previous therapy									
Resistant	5	..	..	..	....	....	....	....	....
Sensitive	16	50	31	19	6.3	6.3	18.9	6.3	6.3
Resistance unknown	23	40	30	30	4.4	8.8	17.6	13.2	4.3

* Based on data presented to the Tenth Conference, January, 1951, Table 11.

SUMMARY

The series of cases of tuberculosis studied by the Veterans Administration, Army, and Navy has increased to about 10,000. For obvious reasons, no attempt is being made to summarize this series here. Rather, an attempt is made to report on the progress of the study, since a somewhat similar report to the Council on Pharmacy and Chemistry was published in March, 1950. The summary can be made in four sentences, the first two containing good tidings, the last two containing, respectively, dubious and bad tidings.

10. Hart, P. D., and Rees, R. J.: Enhancing Effect of Cortisone on Tuberculosis in the Mouse, Lancet **2**: 391, 1950.

11. Spain, D. M., and Molomut, N.: Effects of Cortisone on the Development of Tuberculous Lesions in Guinea Pigs and on Their Modification by Streptomycin Therapy, Am. Rev. Tuberc. **62**: 337, 1950.

12. Michael, M., Jr.; Cummings, M. M., and Bloom, W. L.: Course of Experimental Tuberculosis in the Rat as Influenced by Cortisone, Proc. Soc. Exper. Biol. & Med. **75**: 613, 1950.

13. Nat. Tuberc. A. Tr. **37**: 4 (Jan.) 1951.

14. Personal communications from Drs. William H. Feldman, Lawrence B. Hobson, and William Steenken Jr.

1. Reducing the dosage of streptomycin to 1 gm., either daily or twice a week, has reduced toxicity without impairing therapeutic efficacy.

2. The concomitant daily administration of *p*-aminosalicylic acid has definitely delayed the emergence of streptomycin-resistant tubercle bacilli and has thereby made possible the desired continuation of effective therapy beyond four months, a procedure that is now being explored.

3. Preliminary observations indicate that concomitant administration of *p*-aminosalicylic acid and streptomycin may have further increased the survival rate of patients with meningeal or miliary tuberculosis.

4. Although many antibiotics and other drugs have been studied during the past 18 months, and although several of them undoubtedly have some bacteriostatic action on tubercle bacilli, none of them promises a favorable comparison with streptomycin, much less of being the "wonder drug" frequently mentioned by the press.

BUREAU OF MEDICAL ECONOMIC RESEARCH

MEDICAL CARE PRICES AND THE COST OF LIVING

Frank G. Dickinson, Ph.D., Chicago

Again, in 1950 the Consumers' Price Index, compiled by the United States Bureau of Labor Statistics, was higher than the index of the prices of medical care items. The Consumers' Price Index, which measures monthly the changes since 1935-1939 in the prices of fixed quantities of goods and services normally purchased by moderate-income families in large cities, stood at 171.9 (adjusted); the index of medical care and drugs, a small part of the Consumers' Price Index, was 147.9 (unadjusted). The base period 1935-1939 equals 100.

According to these indexes, which are considered our best general measure of the purchasing power of the consumer's dollar, the price of medical care has risen 48% since 1935-1939 while the general cost of living has risen 72%. Stated another way, a dollar in the base period could buy a dollar's worth of medical care or a dollar's worth of all the goods and services priced for the Consumers' Price Index; a dollar in 1950 could buy only 58 cents' worth (58.2) of all goods and services but 68 cents' worth (67.6) of medical care. Thus, in terms of the purchasing power of the dollar, medical care was 14% cheaper in 1950 than in 1935-1939 (58.2¢/67.6¢ = 86% or 147.9/171.9 = 86%).

In the accompanying table, the Consumers' Price Index is presented along with the price indexes of the medical care items for the years 1947 through 1950.[1] The index of medical care and drugs is divided into two main parts—(I) Medical care, excluding drugs and (II) Prescriptions and drugs. For 1950 the index of medical care excluding drugs was 153.1; the index of prescriptions and drugs was 124.8. The index of physicians' fees (general practitioner, surgeon, specialist) was 140.0; of general practitioners' fees, 139.8, and of surgeons' and specialists' fees, 140.6. The index of dentists' fees was 154.3 and the highest index, 235.3, was for hospital rates. Thus, with the exception of hospital rates, the prices of individual medical care items have risen considerably less than the Consumers' Price Index.

As explained in earlier publications,[1] the high hospital rate index reflects the fact that hospitals are singularly exposed to the forces of inflation. It also must be realized that the period 1935-1939, while generally accepted by economists as a relatively normal period for the purposes of general statistical comparison, is not an equally good base in the case of every item. There is reason to believe that it is a somewhat less appropriate base to use for the measure of the increase in hospital rates. The eight-hour day for nurses in hospitals was first introduced during the early 1930's, but it was not until the late 1930's and early 1940's that it prevailed in most hospitals. Thus, this change in the working day of nurses, which would considerably affect the labor costs of hospitals, was not fully accomplished until after the base period. Other developments, however, might have counterbalanced this one factor. Complete examination of all the factors affecting the choice of a base period is beyond the scope of this article.

The relatively small increase in the price of physicians' services in an inflationary era is to be expected. These prices are influenced by custom and are not as sensitive to changes in the economy as are the prices of most goods and services—particularly those whose prices must cover the costs of many other items used in their production. Physicians' fees belong to a class known as "sticky" prices; they move neither up nor down as rapidly or as far as other prices. The economic position of the physician, however, becomes adjusted to changes in the rest of the economy in other ways. Thus, while physicians' fees had not increased as much as other prices, by 1949 the physician's collections had become so much better and his "output" so much greater that his over-all income had increased since 1935-1939

The Consumers' Price Index and Price Indexes for Medical Care for Moderate-Income Families in Large Cities, for the Years 1947-1950

(1935-1939 = 100)

	1947	1948	1949	1950
Consumers' Price Index (cost of living)..	159.6	171.9	170.2	171.9
(Unadjusted)*	(159.2)	(171.2)	(169.1)	(171.2)
Medical care and drugs.....	131.6	140.1	144.9	147.9†
I. Medical care, excluding drugs.....	135.3	144.4	149.7	153.1
A. Physicians' fees (general practitioner, surgeon, specialist).....	130.2	135.5	137.9	140.0
1. General practitioners' fees.....	130.3	135.2	137.7	139.8
(a) Office visit	131.5	136.9	139.0	140.9
(b) House visit	125.3	128.5	131.4	133.9
(c) Obstetric case	143.7	153.4	155.6	157.3
2. Surgeons' and specialists' fees..	129.4	135.8	138.4	140.6
(a) Appendectomy, adult	128.2	133.1	134.2	137.4
(b) Tonsillectomy, child	130.7	138.7	142.8	144.0
B. Dentists' fees	137.4	144.8	150.6	154.3
1. Fillings	137.7	145.1	150.9	154.5
2. Extractions	139.0	146.8	152.9	156.9
C. Optometrists' fees, eyeglasses.....	118.6	123.6	127.6	128.9
D. Hospital rates	179.6	209.7	226.8	235.3
1. Men's pay ward.....	194.4	231.6	253.5	265.5
2. Semi-private room	175.1	204.2	221.7	229.6
3. Private room	169.7	194.7	207.7	213.7
II. Prescriptions and drugs.....	115.4	121.5	123.3	124.8
A. Prescriptions	123.7	133.9	137.1	140.7

Source: for Consumers' Price Index, Monthly Labor Review, Bureau of Labor Statistics, U. S. Department of Labor, 72:494 (April) 1951; for medical care price indexes 1947-1949, Indexes of Retail Prices of Apparel, Housefurnishings, and Services and Miscellaneous Goods to Moderate-Income Families in Large Cities, Quarterly reports—June 1948, March 1949, and March 1950 and data for 1950 through correspondence, U. S. Bureau of Labor Statistics.

* See text for explanation.

† Subject to revision.

Director, Bureau of Medical Economic Research.

This article was prepared with the assistance of Janice Oberman, Research Assistant, American Medical Association Bureau of Medical Economic Research; Ewan Clague, Commissioner of Labor Statistics, and Ethel D. Hoover, Chief, Branch of Consumers' Prices, Bureau of Labor Statistics, United States Department of Labor.

1. This table is an extension of the tables on medical price indexes in the following publications of the Bureau of Medical Economic Research, American Medical Association: Bulletin 62, Comparative Increases in the Costs of Medical Care and in the Costs of Living, 1948; Bulletin 66, The Cost and Quantity of Medical Care in the United States, 1948; Medical Care Prices vs. Cost of Living, J. A. M. A. **139**: 591 (Feb. 26) 1949, reprinted in Bulletin 67, Four Recent Articles on Medical Economics, 1949; Medical Care Prices vs. Cost of Living, J. A. M. A. **143**: 1198 (July 29) 1950, reprinted as Bulletin 76, 1950.

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just about as much as the national income per capita.[2] In order for the physician to retain the same economic position in a time of rapidly changing price levels, it is not necessary for him to change his price to the extent that other prices have changed.

It should always be kept in mind that an index of prices measures *changes* in the level of prices but does not indicate the level itself for any year or for the base period. The significance and applicability of the Consumers' Price Index and the indexes of the individual items may be somewhat limited by the fact that the prices represented are those for goods and services purchased by moderate-income families in 34 large cities. To the extent that the rise, percentagewise, in prices of goods purchased by low and high income families in all cities corresponds with the price rise, percentagewise, of goods for the moderate-income families in the 34 cities, the indexes reflect price changes for goods purchased by all persons in the United States. Despite these technical limitations this Index is considered the best measure of changes in purchasing power and is widely used to compute cost-of-living wage and salary adjustments.

For the past few years the Bureau of Labor Statistics has been engaged in preparations for a large-scale revision of its price indexes. This revision is designed to modernize the indexes so that they will reflect certain population changes and changes in the buying habits of the American people. It was recognized that many goods which have become an important part of the budget of the moderate-income consumer were not priced or did not exist when the items for pricing were originally selected and that the distribution of weights among the various items has changed considerably during the past few years. In the medical care field, for example, the wonder drugs and the extra services in hospitals, which have become such an important part of medical care, were not included in pricing medical care items. As a preliminary phase of the general revision, which is scheduled to be completed by the middle of 1952, the Bureau of Labor Statistics has undertaken a study to determine the individual goods and services to be included in the revised index.

Originally, no important changes were to be made in the indexes until the general revision was finished. With the outbreak of the fighting in Korea, however, the sharp and diverse price movements and the need for economic stabilization made it necessary to have as accurate a measure of prices as possible. The Bureau of Labor Statistics, therefore, introduced certain immediate improvements and adjustments. No changes in basic concepts or methodology will be made until the final revision. The present adjustments consist chiefly of a revision of city population weights based on the 1950 census, a correction of the "new unit bias" in the rent index, the addition of new items, and a revision of commodity weights. These adjustments have already been made in the calculation of the Consumers' Price Index. The indexes for the individual medical care items have not yet been adjusted.[3] Since the adjusted Consumers' Price Index is the best measure of price change, it is shown in our table (row 1) in place of the former unadjusted data. The unadjusted data have been inserted in parentheses in the second row merely for purposes of comparison; these are slightly lower than the adjusted series.

It is believed that these adjustments and particularly the changes to be made in the final revision of the Index will considerably improve the representativeness of the Index. The Bureau of Medical Economic Research has previously expressed its appreciation of the cooperation shown by physicians, dentists, and hospital administrators in providing the field representatives of the Department of Labor with information regarding fee schedules and charges. In view of the important changes to be made in the Index and the great usefulness of these data to the Bureau, it is hoped that these groups will continue to show their cooperation.

2. Dickinson, F. G., and Bradley, C. E.: Survey of Physicians' Incomes, J. A. M. A. **146:** 1249 (July 28) 1951. Reprinted as Bulletin 84, Bureau of Medical Economic Research, American Medical Association, 1951.

3. The 1950 index for medical care and drug items was not revised when the all-items index was adjusted because the same price relatives for individual items were used in both the adjusted and unadjusted series.

COUNCIL ON PHYSICAL MEDICINE AND REHABILITATION

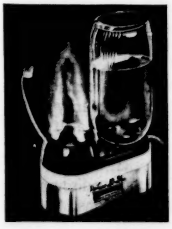
The Council on Physical Medicine and Rehabilitation has authorized publication of the following reports.

RALPH E. DE FOREST, M.D., *Secretary.*

ELECTRESTEEM VAPORIZERS ACCEPTED

Manufacturer: Electric Steam Radiator Corporation, 1 Electric Ave., Paris, Ky.

The Electresteem Vaporizers, Models 10-24 hour Standard and 10-24 hour DeLuxe, are devices for humidifying rooms by heating water and discharging the vapor. The water is heated directly by the passage of an alternating current and is thus evaporated. The heater requires a source of 60 cycle current at 115 volts and draws 350 watts. The generation of heat and liberation of vapor takes place in a small chamber somewhat removed from the main water reservoir, so that only a small amount of water is hot at any given time and the liberation of vapor begins very soon after the electricity is turned on. It will raise the humidity in a small room; more than one unit must be used for a large room.



Electresteem Vaporizer

The specimen submitted by the firm was designed to hold a one-gallon glass jar (3,780 cc.). Its overall dimensions are 27 by 27 by 12 cm. (10¾ by 10¾ by 4¾ in.) and it weighs 1.25 kg. (2¾ lb.). Prepared for shipping it measures 28 by 28 by 13 cm. (11 by 11 by 5 in.) and weighs 1.4 kg. (3 lb.).

Laboratory measurements and evidence from other acceptable sources indicated that the device performed as represented by the manufacturer. The device is listed by Underwriters' Laboratories, Inc. The Council on Physical Medicine and Rehabilitation voted to include the Electresteem Vaporizers, Models 10-24 hour Standard and 10-24 hour DeLuxe, in its list of accepted devices.

PEERLESS HIGH FREQUENCY EPILATION UNIT, NO. 108, ACCEPTED

Manufacturer: Peerless X-Ray Laboratories & Mfg. Corp., 467 Tenth Ave., New York 18.

The Peerless High Frequency Epilation Unit, No. 108, is a device intended for use in the removal of superfluous hairs. The dimensions are 43 by 27 by 20 cm. (17 by 10½ by 8 in.) and the weight is 8.6 kg. (19 lb.). Packed for shipment it measures 51 by 25 by 30 cm. (20 by 10 by 12 in.) and weighs 11.4 kg. (25 lb.). The foreign shipping weight is 18 kg. Accessories, not included in these shipping weights, are a footswitch, hand electrode, electrode wire, needle holder, and a dozen needles. The device requires a source of 50 to 60 cycle alternating current at 110 or 220 volts and draws 50 watts of power. A previous model was accepted by the Council and the acceptance was announced in THE JOURNAL of September 14, 1946.

Peerless High Frequency Epilation Unit, No. 108

Evidence from sources acceptable to the Council indicated that the device was soundly constructed and performed as represented by the manufacturer. The Council on Physical Medicine and Rehabilitation voted to include the Peerless High Frequency Epilation Unit, No. 108, in its list of accepted devices.

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION
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THE LOS ANGELES SESSION OF THE AMERICAN MEDICAL ASSOCIATION

The fifth annual Clinical Session of the American Medical Association, with its scientific program, exhibits, and House of Delegates meetings, will be held in Los Angeles, Dec. 4-7, 1951. The Clinical Sessions, scheduled midway between the Annual Sessions of the Association, have increased in popularity since their inception four years ago. One reason for this popularity is the growing realization among busy clinicians that it is impossible to keep abreast of current developments in medicine without frequent short refresher courses, such as those provided by the clinical lectures, discussions, demonstrations, and exhibits of these sessions. Another is the increasing interest in, and awareness of, the activity of the governing body of the American Medical Association, the House of Delegates, which attracts a larger audience of visitors each year. This year a third reason can be added: the not unpleasant prospect of a brief winter holiday in sunny California.

As in past years the scientific program of the Clinical Session will emphasize the practical application of recent advances in medicine to the everyday problems of general practice. Outstanding clinical teachers will present lectures and demonstrations on such topics as problems in obstetrical delivery, the differential diagnosis of poliomyelitis and Coxsackie virus disease, urologic diagnosis, correctable types of heart disease, dermatologic therapy, psychotherapy, office anesthesia, acute abdominal conditions, head injuries, and allergy.

In the Scientific Exhibit, housed in the Shrine Auditorium, a wealth of information and experience in many branches of medicine will be presented in condensed, graphic form. Several special exhibits on fractures, obesity, and noise, that proved popular at the Atlantic City Session, will be shown again in Los Angeles. The numerous technical exhibits, also located in the Shrine Auditorium, will display a variety of new drugs, books, instruments, and other equipment of use to clinicians. Representatives of the manufacturers will be available to answer questions or discuss the application of these products to the individual physician's problems. Continuous motion picture and television demonstrations of numerous diagnostic and therapeutic procedures will be provided.

One of the high lights of the Clinical Session will be the presentation by the House of Delegates of an award to the General Practitioner of the Year. The recipient of this honor is selected by a vote from among a list of candidates submitted by the county and state medical societies to the Board of Trustees.

Those who have attended these meetings in previous years are aware of the advantages of early registration. All others are urged to make their hotel reservations as soon as possible. Application forms for hotel reservations and for advance registration may be found in this (adv. pp. 14-15) and subsequent issues of THE JOURNAL.

CORTISONE AND TUBERCULOSIS

In 1949 Lurie [1] and his associates of the Henry Phipps Institute, Philadelphia, reported that in rabbits tuberculosis is accompanied by hypertrophy of the adrenal cortex and that the degree of hypertrophy is much greater in genetically resistant strains of rabbits than in susceptible strains. This suggested a positive role of adrenal hormones in tuberculosis resistance. Tests were therefore made [2] of the possible prophylactic or therapeutic action of cortisone on air-borne tuberculosis.

Twenty littermates of a genetically uniform and highly susceptible strain of rabbits were divided into two groups of 10 each. One group received intramuscularly 2 mg. of cortisone acetate per kilogram of body weight on alternate days. The second group received the same volume of suspending fluid without cortisone. Three days after the start of cortisone treatment, when the circulating lymphocytes had been markedly depressed and the fasting blood sugar increased in the cortisone-treated animals, both groups were simultaneously exposed to inhalation of a known number of viable, virulent, human-type tubercle bacilli (H37Rv), by the Lurie [3] technic, for the study of air-borne infections.

All animals were maintained in a room at a constant temperature and the cortisone injections continued till the end of the experiment. Thirty-four to 38 days later, the animals were killed and the number and size of the pulmonary tubercles determined. On an average, four times as many tubercles were found in the lungs of the cortisone-treated animals as in the controls. For example, 275 tubercles developed in the lungs of one treated rabbit and only 72 in the lungs of its control.

The simplest explanation of this difference is that cortisone increases the phagocytic activity of alveolar

1. Lurie, M. B.; Abramson, S., and Allison, M. J.: Constitutional Factors in Resistance to Infection: I. The Effect of Estrogen and Chorionic Gonadotropin on the Course of Tuberculosis in Highly Inbred Rabbits: Am. Rev. Tuberc. **59**: 168 (Feb.) 1949. Lurie, M. B.; Harris, T. N.; Abramson, S., and Allison, M. J.: Constitutional Factors in Resistance to Infection: II. The Effect of Estrogen on Tuberculin Skin Sensitivity and on the Allergy of the Internal Tissues, ibid. **59**: 186 (Feb.) 1949. Lurie, M. B.; Abramson, S.; Heppleston, A. G., and Allison, M. J.: Constitutional Factors in Resistance to Infection: III. On the Mode of Action of Estrogen and Gonadotropin on the Progress of Tuberculosis, ibid. **59**: 198 (Feb.) 1949.

2. Lurie, M. B.; Zappasodi, P.; Dannenberg, A. M., Jr., and Swartz, I. B.: Constitutional Factors in Resistance to Infection: The Effect of Cortisone on the Pathogenesis of Tuberculosis, Science **113**: 234 (March 2) 1951.

3. Lurie, M. B.; Heppleston, A. G.; Abramson, S., and Swartz, I. B.: An Evaluation of the Method of Quantitative Airborne Infection and Its Use in the Study of the Pathogenesis of Tuberculosis: Am. Rev. Tuberc. **61**: 765 (June) 1950.

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macrophages, so that more of the inhaled bacilli are retained than in the control. This belief was confirmed by a quantitative study of splenic and hepatic phagocytosis of carbon particles following intravenous injection of india ink. A similar increase in pulmonary retention of tubercle bacilli had been previously noted in genetically resistant rabbits.[4] The increased phagocytosis, however, does not mean an increased destruction of the bacilli.

While the number of pulmonary tubercles was much greater in the treated animals, each tubercle was much smaller than in the control. In the control rabbits the individual tubercles averaged 5.5 mm. in diameter, while the average in the cortisone-treated rabbits was about 2.5 mm. The tubercles in the cortisone-treated animals were swarming with bacilli, while the control tubercles contained relatively few micro-organisms. Moreover, the spread of the disease to the regional lymph nodes and to other parts of the body was markedly reduced in the treated animals. In this respect, also, the reaction of the cortisone-treated susceptible rabbits was similar to that of the genetically resistant strain, in which tuberculosis develops earlier but which survive longer and have a more localized disease.

CANCER TEACHING IN MEDICAL SCHOOLS

The emphasis now placed on cancer in medical schools has prompted the need for assessment of the relative effectiveness of various teaching methods and the effectiveness of medical educational programs in general. The examination was originally prepared at the University of California in order to evaluate the program for bettering cancer teaching in the medical school.[1] In view of the promising results obtained, a similar test on a nation-wide scale was undertaken in 1949 in consultation with, and with the financial support of, the National Cancer Institute. The test was given to 9,358 students in 32 four-year medical schools in the United States.[2]

The test was of the objective type and consisted of 180 five-choice, multiple-response items which varied greatly in complexity. Efforts were made to sample the whole field of cancer and to avoid controversial matters. The results showed wide differences between the average scores of students from school to school, the differences tending to increase with each succeeding class year. The subject matter was analyzed and the items grouped according to the department of the school considered most responsible for teaching the information tested. These departments were then furnished information indicating how their students answered the questions as compared with all students at a similar academic level. The report reveals that many students graduating today lack important knowledge concerning the diagnosis and treatment of cancer. The results of the test have already proved of benefit in the planning of cancer teaching programs, but only if the tests are given several times can changes in cancer learning be measured. Present plans call for the readministration of the test in all cooperating schools each year for five years. It is hoped that this will give some measure of the gain in student knowledge resulting from the education programs in medical schools throughout the country.

NEUROLOGICAL "FEEDING CENTERS"

Hetherington[1] and others have demonstrated the existence in rats of a hypothalamic nucleus whose destruction leads to a marked increase in food intake, with resulting obesity. This nucleus thus apparently acts as a dietary inhibitor. A second center, which appears to be primarily a feeding center, is currently described by Anand and Brobeck[2] of Yale University. The Yale physiologist tested the effects on food intake of small electrolytic lesions placed by the Horsley-Clarke instrument in other areas of the hypothalamus. Two well-localized areas were found; destruction of both areas was followed by a complete absence of food intake even to the point of death by starvation. After a destruction of one of these foci, rats continue to eat, even if previously made hyperphagic by destruction of the inhibiting nucleus.

The nutritional or hormonal factors serving as primary stimulants of these feeding centers have not been determined. Mayer[3] of Harvard University has suggested that blood sugar acts as the primary hormonal stimulant, a "glucostatic" theory now under investigation.

ARTIFICIAL INSEMINATION

Both here and abroad, more and more consideration is being given to the medicolegal aspects of artificial insemination. A study has been under way for some time by a committee appointed by the Swedish government, which in collaboration with similar committees created in Denmark and Norway is undertaking to prepare uniform Scandinavian legislation to clarify some of the legal uncertainties that arise out of this procedure. Legislation having a similar objective has been considered by a number of states in this country in recent years, but no law has as yet been enacted dealing with the subject. In this issue of THE JOURNAL (page 250) is published an article prepared by the Bureau of Legal Medicine and Legislation which points up some of the significant legal issues that present themselves when a child results from artificial insemination. The article contains references to pertinent court decisions, medicolegal discussions, and types of legislation that have been proposed in the United States. This is a subject the importance of which should be realized by all physicians who undertake artificially to inseminate a woman and is one that merits further study.

---

4. Lurie, M. B.: Experimental Epidemiology of Tuberculosis: Hereditary Resistance to Attack by Tuberculosis and to the Ensuing Disease and the Effect of the Concentration of Tubercle Bacilli upon These Two Phases of Resistance, J. Exper. Med. **79**: 573 (June 1) 1944.

1. Bierman, H. R., and McClelland, J. N.: A Study of Methods for the Improvement of Cancer Learning in the Medical School: First Annual Report, J. A. Am. M. Coll. **24**: 351 (Feb.) 1949.

2. Bierman, H. R., and McClelland, J. N.: An Achievement Examination in the Subject of Cancer for Medical School Students, Pub. Health Rep. **66**: 769 (June 15) 1951.

1. Hetherington, A. W.: The Relation of Various Hypothalamic Lesions to Adiposity and Other Phenomena in the Rat, Am. J. Physiol. **133**: 326, 1941. Non-Production of Hypothalamic Obesity in the Rat by Lesions Rostral or Dorsal to the Ventro-Medial Hypothalamic Nuclei, J. Comp. Neurol. **80**: 33, 1944. Hetherington, A. W., and Ransom, S. W.: The Relation of Various Hypothalamic Lesions to Adiposity in the Rat, ibid. **78**: 475, 1942.

2. Anand, B. K., and Brobeck, J. R.: Localization of a "Feeding Center" in the Hypothalamus of the Rat, Proc. Soc. Exper. Biol. & Med. **77**: 323 (June) 1951.

3. Mayer, J.; Vitale, J. J., and Bates, M. W.: Mechanism of the Regulation of Food Intake, Nature **167**: 562, 1951.

ORGANIZATION SECTION

OFFICIAL NOTES

The abstract of the Proceedings of the 1951 Annual Session of the American Medical Association which appeared in THE JOURNAL for June 30 and July 7 did not include the annual reports of the Treasurer and Auditor. These are presented herewith.

TREASURER'S REPORT

Report of the Treasurer of the American Medical Association for the Year Ended Dec. 31, 1950

Investments (at cost) as at Jan. 1, 1950		$4,716,546.79
Bonds Purchased (at cost)	$1,880,900.32	
Common Stocks Purchased (at cost)	424,071.99	2,304,972.31
		$7,021,519.10
Less:		
Bonds called, matured or sold		2,271,370.62
Investments as at December 31, 1950		$4,750,148.48
Balance held for investment January 1, 1950		33,057.58
Interest and Dividends received on investments in 1950		170,369.90
		$ 203,427.48
Transferred to General Fund		165,675.00
Uninvested Funds as at December 31, 1950		37,752.48
Invested and Uninvested Funds as at December 31, 1950		$4,787,900.96

DAVIS MEMORIAL FUND

Balance in Fund January 1, 1950	$ 8,307.93	
Interest Earned on Bank Balance in 1950	104.15	
Funds on Deposit at December 31, 1950		$ 8,412.08

AMERICAN MEDICAL ASSOCIATION RESEARCH FUND

Investments (at cost) as at January 1, 1950	$1,491,209.38	
Bonds Purchased (at cost)	100,000.00	
	$1,591,209.38	
Less:		
Bonds sold	101,106.25	
Investments as at December 31, 1950		$1,490,103.13
Uninvested funds as at January 1, 1950	$ 2,134.37	
Add:		
Gain from sale of securities	1,862.50	
Uninvested funds as at December 31, 1950		3,996.87
Invested and Uninvested funds as at December 31, 1950		$1,494,100.00
Interest received on investments and transferred to General Fund to apply on Research expenditures	$ 36,834.37	

JOSIAH J. MOORE, Treasurer.

AUDITOR'S REPORT

March 28, 1951

To the Board of Trustees,
American Medical Association,
Chicago, Illinois.

We have examined the balance sheet of American Medical Association as of December 31, 1950 and the related statement of income for the year then ended. Our examination was made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the accompanying balance sheet and statement of income present fairly the financial position of American Medical Association at December 31, 1950 and the results of its operations for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent in all material respects with that of the preceding year.

PEAT, MARWICK, MITCHELL & CO.

BALANCE SHEET

AS OF DEC. 31, 1950

ASSETS

Cash in Banks and on Hand			$ 151,762.13
Accounts Receivable:			
Advertising	$ 270,199.74		
Reprints	14,268.14		
Directory Report Service—19th Edition	45,556.17		
Miscellaneous	25,605.25		355,629.30
Interest Accrued on Investments			32,865.96
Inventories of Materials, Supplies, Work in Progress, and Publications—At cost			340,048.07
Expenditure on Publications in Progress			62,976.32
Prepaid Expenses, Deposits and Advances:			
Advances to cover commitments of the National Education Program	45,505.99		
Other deposits and advances	30,649.22		
Insurance and other prepaid expenses	15,258.17		91,413.38
Marketable Securities—At cost (value based on market quotations, $4,736,973.68):			
United States Government securities	2,523,188.28		
Railroad, municipal, public utility and industrial bonds	1,802,888.21		
Common stocks	424,071.99		4,750,148.48
Representing investments of:			
American Medical Education Foundation Fund	500,000.00		
General Fund	700,148.48		
Depreciation Reserve Fund	1,375,000.00		
Association Reserve Fund	350,000.00		
Retirement Reserve Fund	675,000.00		
Building Reserve Fund	450,000.00		
Equipment Modernization Reserve Fund	700,000.00		
American Medical Association Research Fund:			
United States Government securities—At cost (value based on market quotations, $1,446,911.88)	1,490,103.13		
Cash in bank	3,996.87		1,494,100.00
Property, Plant and Equipment—At cost:			
Land	328,773.98		
Building	$2,108,893.30		
Machinery and printing equipment	646,119.25		
Office and laboratory equipment	419,726.55		
	3,174,739.10		
Less—Reserve for depreciation	1,374,336.26	1,800,402.84	2,129,176.82
			$9,408,120.46

See notes to statement of income.

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LIABILITIES

Accounts Payable and Accrued Expenses:		
State Journal Advertising Bureau		$ 53,207.05
Miscellaneous accounts payable		196,020.68
Taxes withheld from employees		32,784.38
Accrued payroll		41,167.09
Accrued taxes:		
Social security	$ 10,199.65	
Real estate and personal property	58,750.00	68,949.65
		392,128.85
Provision for Payment to American Medical Education Foundation		500,000.00
Provision for Completion Costs of Publications to be issued		172,461.60
Deferred Credits:		
Unexpired subscriptions to publications	376,884.88	
Income from 19th edition directory report service less accumulated costs applicable to directory	26,966.87	
Dues paid in advance	2,580.00	406,431.75
American Medical Association Research Fund Reserve		1,494,100.00
Other Reserves:		
Association	350,000.00	
Retirement	675,000.00	
Building	450,000.00	
Equipment modernization	700,000.00	2,175,000.00
Capital Account:		
Balance at December 31, 1949	4,240,197.81	
Excess of income over expenses for year ended December 31, 1950	27,800.45	4,267,998.26
		$9,408,120.46

STATEMENT OF INCOME

FOR THE YEAR ENDED DECEMBER 31, 1950

Income:		
Membership dues for 1950, less $2,346,955.58 allocated to National Education Program		$ 308,829.42
Fellowship dues		70,319.00
Income from investments		169,520.81
Miscellaneous receipts and other income		40,312.10
		588,981.33
Publications (Periodicals):		
Subscriptions	$2,315,212.39	
Advertising	2,599,306.74	
	4,914,519.13	
Less—Cost and expenses	3,174,818.86	1,739,700.27
National Education Program:		
1949 assessments collected in 1950	70,284.50	
Unexpended assessments collected in 1949, reserved at December 31, 1949 for 1950 expenditures	676,145.45	
Amount allocated from 1950 membership dues	2,346,955.58	
	3,093,385.53	
Deduct:		
Expenditures for National Education Program	$2,593,385.53	
Appropriated for American Medical Education Foundation	500,000.00	3,093,385.53
		2,328,681.60
Expenses:		
Councils, bureaus and related activities	1,838,381.85	
Accumulated expenses of publishing American Medical Directory, 18th Edition, in excess of accumulated income therefrom	43,161.86	
Accumulated expenses and provision for completion costs of publishing Quarterly Cumulative Index in excess of accumulated income therefrom	71,877.65	
Costs and other expenses of printing and procuring books, pamphlets and reprints in excess of income therefrom	57,104.59	
Annual and interim sessions—Net	72,214.47	
Employees' past service annuities and allowances	135,546.80	
Cash discounts—Net	36,104.66	
Depreciation and taxes unallocated	32,160.65	
Legal and sundry	14,328.62	2,300,881.15
Income in Excess of Expenses		$ 27,800.45

Notes:

1. The records of the Association are maintained substantially on an accrual basis with the exception that income from current membership dues is recorded when received. Collections of 1950 dues subsequent to December 31, 1950 amounted to $180,600.00 at March 27, 1951.
2. During the year 1950, the Association revised the classification of certain of its accounts with the result that individual items are not entirely comparable with similar items of the previous year.

PUBLICATIONS (PERIODICALS) COSTS AND EXPENSES

FOR THE YEAR ENDED DECEMBER 31, 1950

Salaries and wages	$1,225,427.99
Paper and ink	674,848.83
Illustrations	79,245.45
Contract printing	127,069.71
Postage and cartage	193,102.11
Editorial (excluding wages)	132,446.75
Advertising sales and services (excluding wages)	95,946.92
Circulation (excluding wages)	364,429.63
Other costs—Including building and plant maintenance, depreciation, taxes and employee welfare tax	282,301.47
	$3,174,818.86

EXPENSES OF COUNCILS, BUREAUS AND RELATED ACTIVITIES

FOR THE YEAR ENDED DECEMBER 31, 1950

Salaries and wages	$ 972,862.21
Office printing	63,985.93
Office supplies and equipment maintenance	40,650.86
Postage, express and freight	29,747.15
Telephone and telegraph	15,247.74
Memberships, books and periodicals	10,930.13
Legislative services	5,119.44
Statistical equipment rental	28,339.41
Membership records and reimbursement to State societies for dues collections	47,269.93
Biographical records	72,176.77
Staff and officers' travel	84,649.86
Inspection of hospitals and medical schools	13,405.96
General administrative expense including allocation of headquarters maintenance, employee insurance and taxes	180,501.62
Educational exhibits and literature	13,112.50
Radio and transcriptions	58,916.57
Trustee meetings	30,190.25
Conferences and meetings	55,641.34
Grants, tests and surveys	33,893.67
Sundry committee meetings	64,463.83
Miscellaneous	17,276.68
	$1,838,381.85

NOTE.—The above Expenses are Allocated to the Following Councils, Bureaus and Related Activities:

Association	$ 206,916.19
Department of Public Relations	102,115.95
Washington Office of A. M. A.	158,159.93
Biographical Records	72,176.77
Membership Records	47,269.93
Survey of Medical Education	58,239.25
A. M. A. Laboratory	72,149.95
Council on Medical Education and Hospitals	177,766.69
Council on Medical Service	89,327.86
Council on Pharmacy and Chemistry	135,468.86
Council on Physical Medicine and Rehabilitation	49,070.62
Council on Foods and Nutrition	36,035.47
Council on Industrial Health	64,626.15
Council on National Emergency Medical Service	36,721.47
A. M. A. Library	48,715.24
Bureau of Exhibits	38,181.56
Bureau of Health Education	150,578.01
Bureau of Investigation	20,148.90
Bureau of Legal Medicine and Legislation	52,721.98
Bureau of Medical Economic Research	140,311.28
Committee on Cosmetics	13,351.50
Committee on Rural Health	34,621.61
Committee on Therapeutic Trials	12,495.64
Committee on Therapeutic Research	7,998.13
Committee on Research	13,212.91
	$1,838,381.85

CIVIL DEFENSE

National Civil Defense Medical Conference

On Nov. 9 and 10, 1951, the American Medical Association will sponsor, with the American Hospital Association and the Association of State and Territorial Health Officers, a National Civil Defense Medical Conference. One of the primary purposes of the meeting, which will be held in Chicago, is to bring together the state health officer, the top state hospital administrator, and the most active member, in terms of civil defense, from each of the state medical associations. The Federal Civil Defense Administration is also actively assisting in preparing the program. They have assured the American Medical Association that by the date of the meeting it will be possible to present several new concrete recommendations, rather than discuss future plans.

Federal Civil Defense Administration Uses Film "They Also Serve"

The film "They Also Serve," which the Council on National Emergency Medical Service of the American Medical Association assisted in preparing, was used in a television series on civil defense, which has appeared for the past several Sundays over the National Broadcasting System. Mr. Howard R. H. Johnson, chief, Motion Picture Branch, Federal Civil Defense Administration, in a letter dated July 25, 1951, said in part: "We used several sequences from your fine film to illustrate the importance of medical services in the event of enemy attack. These film sequences made a real contribution to the program."

Recent Publications Regarding Civil Defense

The Council on National Emergency Medical Service of the American Medical Association has compiled the following list of articles and publications regarding the medical aspects of civil defense:

Medical Aspects of Nuclear Energy
Army-Navy-Air Force Register, July 21, 1951

Radiation Hazards
Statement by Gen. James Cooney, *Chicago Medical Society Bulletin,* July 14, 1951

What If an A-Bomb Hits Chicago Water Supply
Engineering News-Record, April 26, 1951

Mass Immunization Program
Orange County California Association Bulletin, July, 1951

Civil Defense issue of the *Bulletin of the Department of Health, Kentucky,* July, 1951

Ophthalmologic Survey of Atomic Bomb Survivors in Japan, 1949
Extract from *Transactions of the American Ophthalmological Society,* 1950, Vol. 48

A Medical Organization for Milwaukee's Civil Defense
Milwaukee Medical Times, July, 1951

First Aid and Rescue Squads of Bergen County
Bulletin of Bergen County Medical Society, April, 1951

Civil Defense—The Integration of Units
San Francisco Medical Society Bulletin, August, 1951

How Hospitals Can Prepare for A-Bomb
Extract from *Hospital Management,* March, 1951

Hospitals' Grim Role in Atomic Attack
Extract from *Hospital Management,* March, 1951

Emergency Medical Planning for the Unprecedented and the Unknown
Extract from *The American City,* July, 1951

Emergency Medical Care if Disaster Strikes
Extract from *The American City,* July, 1951

Assignment of Physicians
Extract from the *Fresno, Calif., Medical Bulletin,* August, 1951

FEDERAL MEDICAL LEGISLATION

Armed Forces Reserves

Senator Russell of Georgia introduced S. 1991 relating to the reserve components of the Armed Forces. This bill is identical with H. R. 4860 (previously reported) and would rewrite the laws pertaining to the reserve organizations of the military services. It would establish the Ready Reserve, Stand-by Reserve, and Retired Reserve.

Problems of the Aging

Representative Rhodes of Pennsylvania introduced H. R. 393. It would authorize a Select Committee on Problems of the Aging to be composed of seven members of the House of Representatives, all appointed by the Speaker. The study committee would investigate the status of the older age group with respect to the manpower potential and the basic problems of this group in the fields of employment, health, education, and community services, and the federal government's responsibilities. It is identical with H. Res. 238 (previously reported).

The summary of federal legislation was prepared by the Washington Office of the American Medical Association.

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MEDICAL NEWS

ARIZONA

Psychotherapy Meeting.—The Coconino County Medical Society is sponsoring a regional meeting of the five northern county medical societies at Grand Canyon Oct. 3. The entire program will deal with psychotherapy in general medicine. Informal round table discussions will follow brief presentations by guest speakers Dr. Hale F. Shirley from the Stanford University School of Medicine, San Francisco, and Dr. Henry Cyril Schumacher, regional consultant in mental hygiene and psychiatry in the United States Public Health Service. Dr. Clarence G. Salsbury of the state health department will act as moderator.

CALIFORNIA

Personal.—Dr. Edward S. Rogers, professor of public health and medical administration on the Berkeley campus of the University of California, has been appointed a member of the Expert Advisory Panel on Health Statistics of the World Health Organization.

Postgraduate Symposia on Heart Disease.—These programs, scheduled for Oct. 19-20 at the Wilshire Ebell Theatre in Los Angeles and Oct. 24-27 at the St. Francis Hotel, San Francisco, are sponsored by the San Francisco and Los Angeles heart associations and are coordinated by the California Heart Association. The programs will include courses in unipolar electrocardiography and heart disease in childhood. There will be panel discussions on cardiac auscultation, medical and surgical aspects of correctable cardiovascular lesions, and arteriosclerosis and its sequelae. The guest speakers will be Dr. Dickinson W. Richards Jr., New York, Lambert Professor of Medicine, Columbia University College of Physicians and Surgeons, who will speak on "Mitral Commissurotomy: Indications for Surgery and Measurements of the Circulation Before and After Operation," and Dr. Howard B. Sprague, Boston, immediate past president of the American Heart Association, also clinical associate in medicine at Harvard Medical School, whose subject will be "Resistive Congestive Failure."

FLORIDA

State Cancer Council.—A seven-man Cancer Control Committee has been formed to unify and help direct cancer control activities in Florida. Representing the Florida Medical Association are Drs. Frazier J. Payton, Miami, and Dr. George W. Morse, Pensacola; representing the State Board of Health, Drs. Wilson T. Sowder and Lorenzo L. Parks, Jacksonville; representing the American Cancer Society, Drs. Ashbel C. Williams, Jacksonville, and Dr. C. Frank Chunn, Tampa, and representing the American College of Surgeons, Dr. Duncan T. McEwan, Orlando.

ILLINOIS

State Distribution of Biological Preparations.—Enough biological preparations to protect more than 1½ million persons against illnesses of various types were distributed by the Illinois State Department of Public Health during the fiscal year ending June 30. This total includes smallpox vaccine for more than 400,000 persons, diphtheria toxoid for 325,000 persons, tetanus toxoid for 315,000, whooping cough vaccine for 240,000, typhoid vaccine for 145,000, and rabies vaccine for 3,426. Enough silver nitrate was distributed to treat the eyes of every baby born in the state. A large volume of biologicals for testing purposes was also provided, including tuberculin for testing 400,000 persons and Schick-testing material for more than 265,000 persons. This entire program of distribution of biologicals cost $223,777, or about 2½ cents per person in Illinois.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education and public health. Programs should be received at least three weeks before the date of meeting.

Chicago

Health Court Created.—A health court specializing in violations of the antiragweed ordinance was established Sept. 4 by Chief Justice Edward S. Scheffler of the municipal court, to expedite the city's fight against hay fever. The court will operate on a full time basis during the hay fever season and will be revived each summer. Heavy fines will be levied against property owners failing to cooperate with city officials in cutting ragweed twice a year on vacant property. On Aug. 27 the city building department had 800 complaints awaiting trial and was making property title searches on 1,000 other complaints.

Army Testing Primaquine for Malaria.—Dr. Alf S. Alving, professor of medicine in the University of Chicago, is flying to Tokyo to direct an Army confirmatory test of the curative value of the anti-malaria drug primaquine on returning Korean veterans. Primaquine, newly developed synthetic, was extensively tested on volunteer prisoners at the Stateville, Ill., penitentiary by Dr. Alving in a program made possible by the cooperation of Warden Joseph Ragen. In this and subsequent studies the drug was highly effective as a malaria cure. Although the Army has successfully controlled malaria in Korea with suppressive drugs, a considerable number of returned veterans have relapsed after the suppressive drugs have been withdrawn. Dr. Alving will test the curative effects of primaquine in veterans being rotated home and will study reactions to the drug.

Museum Medical Lectures.—The fall lecture series at the Museum of Science and Industry is presented with the cooperation of the medical committee for the museum appointed by the University of Illinois. The lectures are scheduled for each Sunday afternoon at 3 o'clock, Sept. 16 through Oct. 21 as follows:

Sept. 16, Hay Fever, Cause and Treatment, Harry L. Huber, University of Chicago.
Sept. 23, Heart Disease, Public Enemy No. 1, Frederick W. Fitz, Northwestern University.
Sept. 30, Rehabilitation of the Crippled, William J. Schnute, Illinois Association of the Crippled.
Oct. 7, In Search of the Soul, Percival Bailey, University of Illinois.
Oct. 14, Overweight, Nutrition and Health, Robert W. Keeton, University of Illinois.
Oct. 21, Modern Miracles in Medicine, Austin Smith, Editor, THE JOURNAL.

KANSAS

Authentic McDowell Painting.—An original early American portrait of Dr. Ephriam McDowell, the first ovariotomist, has been acquired by the Clendening Library of Medical History at the University of Kansas, Kansas City. This oil painting, which was done by William Davenport in Danville, Ky., in 1829, just two years before the death of Dr. McDowell, came to Missouri with the doctor's descendants in 1858. Within the past two years, it was rediscovered in the home of the late Dr. Cyrus Cantrell of Kansas City, who had been feted as the leading general practitioner of 1949 in the greater Kansas City area. After the doctor's death early in 1951, Mrs. Cantrell gave the portrait to the Clendening Library. The authenticity of this painting is accepted by Dr. Lewis J. Moorman, Oklahoma physician, in his recently published autobiography, "Pioneer Doctor." A more recent copy of this portrait hangs over the mantelpiece of McDowell's Danville home, which has been restored as a shrine by the Women's Auxiliary of the Kentucky State Medical Association.

KENTUCKY

Grant for Study on Poliomyelitis.—Dr. Alexander J. Steigman, professor of child health at the University of Louisville School of Medicine, is the recipient of a $23,635 grant-in-aid from the National Foundation for Infantile Paralysis, Inc., for studies on experimental poliomyelitis.

LOUISIANA

Personal.—Dr. William A. Sodeman, chairman since 1946 of the department of tropical medicine and public health in the Tulane University of Louisiana School of Medicine, New Orleans, has been awarded a Fulbright lectureship grant at the Calcutta, India, school of tropical medicine. Teaching both clinical and tropical medicine, Dr. Sodeman will remain at the Calcutta school for one year.

Dr. Harris to Head Physiology Department.—Dr. A. Sidney Harris of Baylor University College of Medicine, Houston, Texas, has accepted an appointment as professor of physiology and chairman of the department of physiology at Louisiana State University College of Medicine, New Orleans. Dr. Harris has been associate professor of physiology at Baylor since 1947. He assumed his new duties Sept. 1.

MARYLAND

Personal.—Dr. George A. Silver, health officer of the Baltimore City Health Department since 1948, has been appointed full-time chief of the division of social medicine at Montefiore Hospital for Chronic Diseases, New York.

Library Gets Cullen Papers.—The collected papers, manuscripts, and published texts of Dr. Thomas S. Cullen, emeritus professor of gynecology at Johns Hopkins University School of Medicine, Baltimore, have been deposited in the Enoch Pratt Free Library, Baltimore. Dr. Cullen has been a library trustee since 1915 and president of the board since 1938. The papers, representing 60 years of work, are considered by Richard Hart, head of the literature department, to be of "extreme value to students of medical history, particularly in gynecology." Dr. Cullen has been associated with Johns Hopkins since 1891 when he was assistant to the late Dr. Howard A. Kelly.

MASSACHUSETTS

Hospital News.—Ground was broken July 11 for the new 7 million dollar St. Vincent Hospital to be built in Worcester and operated by the Sisters of Providence. The seven-story 400-bed hospital and adjoining convent are expected to be complete in two years when the present hospital will be remodeled for the care of the chronic sick and for specialized maternity service.

Industrial Physicians' Meeting.—Handling of radioactive materials in industry and the employment of the mentally and emotionally maladjusted and the orthopedically handicapped are the problems to be considered by industrial physicians meeting at the Hotel Bradford in Boston, Oct. 17, under the auspices of the Committee on Industrial Health of the Massachusetts Medical Society. More than 300 industrial physicians are expected to attend.

MICHIGAN

Hospital Dedicated.—The new 2 million dollar Memorial Hospital in St. Joseph was dedicated July 22, climaxing five years of planning, fund raising, and construction. The 104-bed hospital erected through about 3,500 contributions from business firms and individuals in the community, was dedicated as a memorial to the men of the St. Joseph area who gave their lives in World War II. The hospital is managed by a nonprofit organization known as the St. Joseph-Benton Harbor Memorial Hospital Association, made up of men of the area representing practically every walk of life in the community.

Cancer Conference.—The third Michigan Cancer Conference will be held Oct. 12 at the W. K. Kellogg Center for Continuing Education on the campus of Michigan State College, East Lansing. It will immediately follow the Annual Training School of the Michigan Division, American Cancer Society, and will be co-sponsored by the two Michigan Divisions of the American Cancer Society, the Michigan Department of Health, and the Michigan State Medical Society. The general theme of the conference will be individual participation in cancer control. Mrs. Marjorie Karker of the Michigan Farm Bureau will speak on "Rural Organizations and the Cancer Problem," and Dr. Madge Thurlow Macklin, Columbus, Ohio, will discuss the "Place of Heredity in Cancer Development." Other conference subjects and speakers will be "Home Care of Cancer Patients: Nursing Problems" by Miss Hulda Edman, cancer nursing specialist of the Detroit Visiting Nurse Association; "Home Care of Cancer Patients: Psychiatric Problems" by Dr. Henry H. Sadler, Grosse Pointe, and "Cancer Education in the Schools" by Dr. Frank L. Rector, secretary, Cancer Control Committee, Michigan State Medical Society, who has been supervising the cancer educational program in several Michigan high schools. All statewide health minded organizations have been invited to send representatives to this meeting. In addition, anyone interested in cancer control will be welcome.

State Society Purchases New Home.—Executive offices of the Michigan State Medical Society in Lansing, have been moved to a new location, according to an announcement made by Dr. L. Fernald Foster, Bay City, secretary. The move was made in late July from the Olds Tower, an office building in downtown Lansing, to a large three-story house at 606 Townsend St., located a few blocks from the downtown area. The society purchased the house when the rapidly expanding executive staff outgrew its old quarters.

New headquarters for the State Medical Society.

MISSOURI

Fall Clinical Conference.—This annual conference of the Kansas City Southwest Clinical Society will be held Oct. 1-4 in the Municipal Auditorium, Kansas City. Guest speakers, together with one of their subjects, are as follows:

Alfred W. Adson, Rochester, Minn., Indications for and the Evaluation of Operations Employed in the Treatment of Malignant Hypertension.
Edward F. Bland, Boston, Course and Complications of Rheumatic Heart Disease, with Special Reference to Management.
John W. Cline, San Francisco, The Responsibility of the Individual Physician.
Warren H. Cole, Chicago, Intestinal Obstruction.
Mims Gage, New Orleans, Malignant Melanoma.
Ross Golden, New York, Problem of Carcinoma of the Stomach.
Verne R. Mason, Beverly Hills, Calif., Pulmonary Fibrosis.
William F. Mengert, Dallas, Texas, Trends in Diagnosis and Treatment of Cervical Carcinoma.
Harold A. O'Brien, Dallas, Texas, Carcinoma of the Prostate.
Herman E. Pearse, Rochester, N. Y., Peripheral Vascular Diseases.
H. Marvin Pollard, Ann Arbor, Mich., Modern Therapy for Gastroduodenal Ulcer.
Heyworth N. Sanford, Chicago, Anemias of Childhood.
George Saslow, St. Louis, Relation Between Personality and Some Gastrointestinal Disorders.
John R. Schenken, Omaha, Pathologic Lesions in the Heart in the Common Types of Heart Disease.
Isaac S. Tassman, Philadelphia, Ocular Manifestations in Diseases of the Vascular System.
Edward B. Tuohy, Washington, D. C., Anesthetic Emergencies and Their Management.

The program also includes a clinical pathologic conference and medical and surgical round table discussions daily at luncheons. Scientific and technical exhibits will be shown.

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NEW YORK

Postgraduate Lecture.—Dr. Arthur C. DeGraff, New York, will speak on "Modern Trends in the Management of Heart Failure" at a meeting of the Onondaga County Medical Society at 8:30 p. m. Oct. 2 at the University Club in Syracuse. This lecture is provided by the Medical Society of the State of New York in cooperation with the New York State Department of Health.

State Health Department Fellowships.—The New York State Department of Health is offering fellowships in public health to young physicians interested in public health as a career. Completion of the required training qualifies the physician for a full-time public health position in New York State. Field and academic training are the two main constituents of the fellowship program. Field training for one year is obtained in a residency in public health with the state health department. Academic training consists of one year at an approved school of public health. Usually six months field training is required before assignment to such a school. The fellowship is for 24 months or less, depending on the qualifications of the fellow at the time of beginning training. Appointment can be made at any time during the year. The monthly stipend allowed during the field training is $350. During the academic training it is $350 per month for fellows with dependents and $200 for those without dependents. In addition, authorized travel, other necessary expenses, and tuition to the school are paid. On completion of training the physician is expected to accept a public health position in New York State. Further details and applications may be obtained from the Office of Professional Training, New York State Department of Health, Albany 1.

New York City

Child Guidance Conference.—The Bureau of Child Guidance of the Board of Education in New York City schools will hold an all-day 20th anniversary conference Oct. 27 at the Hotel Astor. Seven panel meetings will make up the morning session and will deal with various phases of "Child Guidance in a Changing World." Panel subjects are The Clinical Approach to Children's Problems; Fear of School; The Adolescent Today; The Teacher in the Mental Health Team; The Contribution of Mental Hygiene to Parenthood; Education for Emotional Maturity, and Mental Hygiene in High Tension Areas. The program is open to professional personnel, teachers, and parents.

Pediatric Research Grants.—Four additional pediatric research grants have been made by the Playtex Park Research Institute. A three-year $15,000 grant has been made to the New York University-Bellevue Medical Center for studies of amino acid metabolism with particular reference to the influence of adrenal and adrenotropic hormones. Studies of blood vessel grafts and vascular shunts in pediatric surgery will be carried out under a three-year $18,000 grant to Montefiore Hospital for Chronic Diseases. The studies will be aimed particularly at the correction of congenital and acquired lesions of the heart and blood vessels; the permitting of a more aggressive approach to removal of tumors, both benign and malignant, and the increasing of the blood supply to organs impaired either organically or functionally. A study of the status at birth and the developmental pattern of kidney function in normal infants and in those with renal or metabolic disorders will be made at the Cornell University Medical College during the next three years under a $15,000 grant from the institute. Hormonal control of water and electrolyte balance in premature infants, older infants, and children will be carried out during the next two years by the department of pediatrics and pharmacology, College of Physicians and Surgeons, Columbia University, under a $10,000 grant from the institute. The institute was founded a little more than a year ago and has made 12 previous grants for pediatric research.

PENNSYLVANIA

Survey of Emergency Medical Service.—Fifty-four areas in Pennsylvania are now covered by 24-hour emergency medical service, according to the latest survey made by the Medical Society of the State of Pennsylvania. These areas include the entire counties of Philadelphia, Allegheny, Lackawanna, Adams, Dauphin, and Delaware, and such cities as Erie, Altoona, Johnstown, Lancaster, and Pottsville. In addition, 25 counties now have some type of emergency medical call service. The oldest service is that of Philadelphia, which has had its Physicians and Surgeons Exchange for 30 years. Many rural and semi-rural areas, the society's survey reveals, do not need emergency medical call service. The few residents of these areas use the services of their own family doctors who are available and willing to respond to call when needed.

State Medical Meeting.—Pittsburgh will be host to more than 2,000 physicians when the annual session of the Medical Society of the State of Pennsylvania meets at the William Penn Hotel Sept. 16-20. A total of 125 physicians will address the scientific sessions on diagnostic and therapeutic advances in all phases of medicine. Twenty guest speakers from New York, Chicago, Boston, and St. Louis will take part. Dr. John W. Cline, San Francisco, President, and Dr. W. W. Bauer, Chicago, Director of the Bureau of Health Education, American Medical Association, will discuss sociomedical problems of the medical profession. Technical and scientific exhibits will be shown. The Benjamin Rush Awards will be presented at the state dinner on Monday to the lay individual and the lay organization which have been judged as contributing most to the health of Pennsylvania during the past year. Dr. Louis W. Jones, Wilkes-Barre, will be installed as president of the society for the ensuing year. The Woman's Auxiliary will meet at the Roosevelt Hotel.

Philadelphia

Dr. Buerki Goes to Detroit.—Dr. Robin C. Buerki has resigned as vice president in charge of medical affairs at the University of Pennsylvania to become executive director of the Henry Ford Hospital, Detroit. He will assume his duties Oct. 1. Dr. Buerki will succeed Dr. Roy D. McClure, who died March 31.

TENNESSEE

Postgraduate Medical Assembly.—The Nashville Academy of Medicine will present its postgraduate medical assembly at the Maxwell House Hotel Oct. 3-5. Out of state speakers include the following:

Michael L. Mason, Chicago, Prevention and Treatment of Infections of the Hand.
Warren W. Quillian, Coral Gables, Fla., Pyurias in Childhood.
M. Edward Davis, Chicago, Modern Management of the Placental Stage and Postpartum Hemorrhage.
Edgar Hull, New Orleans, Cardiac Emergencies and Their Management.
Keith S. Grimson, Durham, N. C., Use of Sympatholytic and Parasympatholytic Drugs.
Harold A. O'Brien, Dallas, Bladder Irritation in Women.
A. McGehee Harvey, Baltimore, The Current Status of ACTH and Cortisone in Medical Practice.
Robert J. Crossen, St. Louis, Gynecological Problems of Interest to the General Practitioner.
John Martin, Chicago, Neurosurgical Procedures for the Relief of Intractable Pain.
Tinsley R. Harrison, Birmingham, Ala., Practical Aspects of Palpitation.
Jack G. Kerr, Dallas, Management of Some Minor Anorectal Lesions.

Dedicating Ceremonies.—Seven medical scientists will be on the program when the University of Tennessee College of Medicine holds a dedication ceremony in Memphis Oct. 4. The observance will mark the completion of the new Cancer Research Laboratory and the six-story Institute of Pathology, a $4,800,000 building program to be launched soon, and the centennial of continuous medical education in Tennessee. Speakers in the morning session, to be held in the auditorium of the Institute of Pathology adjacent to John Gaston Hospital, are Dr. Robert A. Moore, dean of Washington University School of Medicine, St. Louis; Alan T. Waterman, Ph.D., director of the National Science Foundation, Washington, D. C., and Dr. Leonard A. Scheele, Surgeon General, United States Public Health Service, Washington. Dr. Moore will speak on "The Place of Pathology in Medical Education." The role a national foundation plays in the progress of medicine will be discussed by Dr. Waterman, and Dr. Scheele will speak on the part that government agencies play in medical research. Speakers on the afternoon program will be Dr. Cornelius P. Rhoads, director of the Memorial Center for Cancer and Allied Diseases, New York, whose topic will be "Recent Advances and Future Possibilities of Cancer Research"; Dr. Henry K. Beecher, professor of research in anesthesia at Harvard Medical School, Boston, who

will discuss effects of wounds on the circulation, and Dr. Edward A. Doisy, director of the biochemistry department of Saint Louis University School of Medicine, who will speak on "Some Aspects of Steroid Metabolism." Dr. John W. Cline, San Francisco, President of the American Medical Association, will deliver the principal address at an evening session at the Peabody Hotel. He will discuss the course medical education should take in the immediate future.

WEST VIRGINIA

Broadcasts on Venereal Disease.—Transcriptions of broadcasts on the control of venereal disease, which will be featured each Monday from 10:30 to 11:00 p. m. over station WTIP, Charleston, will be made available for use on all radio stations in West Virginia. The 14-week series will begin Sept. 10. The first 15 minutes of each broadcast will consist of a drama; the last 15 minutes will include a timely talk by personnel from the state department of health, local health officers, doctors in practice in the state, county superintendents of schools, and ministers. A question and answer period will conclude each program. The final broadcast will include a panel discussion with program participants appearing. The series is made possible by the Charleston Chapter of the Council of Jewish Women in cooperation with the state department of health.

Rural Health Conference.—The fourth annual rural health conference, sponsored by the West Virginia State Medical Association, will be held at Jackson's Mill Sept. 28. The theme for the conference will be community health councils. The program will include addresses by speakers of state and national reputation, and a panel discussion following the afternoon program will be led by Dr. John F. McCuskey of Clarksburg and Dr. Paul L. McCuskey of Parkersburg, co-chairmen of the state public relations committee. The meeting will be attended by representatives of the agricultural extension service of West Virginia University, the state grange, farm bureau, farm women's council, state health department, West Virginia University School of Medicine, and other state groups. Those attending the conference will be guests of the state medical association at a luncheon in the Mount Vernon dining hall.

WISCONSIN

Waupun Memorial Hospital.—This 60-bed hospital, built without federal aid, was opened early in July. The School Sisters of St. Francis, with headquarters in Milwaukee, took over the $1,750,000 project. It is to be operated as a public hospital and is a memorial to the service men and women of both World Wars. The towns of Alto and Chester also contributed to the construction.

State Chest Physicians Meeting.—The Wisconsin chapter of the American College of Chest Physicians will meet at the Hotel Schroeder the afternoon of Sept. 30 preceding the meeting of the State Medical Society of Wisconsin. Visiting speakers include the following:

Jay A. Myers, Minneapolis, Primary Tuberculosis in Adults.
Chevalier L. Jackson, Philadelphia, Significance of the Bronchopulmonary Segments.
Burgess L. Gordon, Philadelphia, Physiological Considerations in the Diagnosis and Management of Chronic Pulmonary Diseases.

GENERAL

Southeastern Surgical Congress.—The northeastern section of the Southeastern Surgical Congress met at the Lord Baltimore Hotel in Baltimore Sept. 13-15. The program included a panel discussion on the effect of prostatectomy on hypertension, the discussions being presented by Dr. Austin I. Dodson, Richmond, Va., and Drs. Alan J. Chenery and James W. Choate, Washington, D. C. A series of 18 papers was read.

Pathologists Get Standardized Testing Solutions.—Greater accuracy in laboratory diagnosis is expected from a service recently announced by the College of American Pathologists. The college is initiating a program enabling pathologists who direct laboratories to obtain highly standardized chemical solutions for use in performing tests on body fluids. By checking solutions prepared by their own technicians against the standard solutions supplied them, laboratory directors can increase the reliability of their medical tests, to the immediate benefit of the sick. Distribution of standardized dextrose and nitrogen solutions to 1,450 member pathologists, which began Aug. 30, marks the initial step in the development of a comprehensive program for standardization of laboratory procedures.

Life Insurance Medical Directors Meeting.—The Association of Life Insurance Medical Directors of America will convene Oct. 11-12 at the Hotel Statler in New York under the presidency of Dr. Lauritz S. Ylvisaker of Philadelphia. Guest speakers include the following:

Philip S. Hench, Rochester, Minn., Cortisone and ACTH.
Francis R. Dieuaide, New York, Progress in Cardiovascular Research.
Harold M. Marvin, New Haven, Conn., Chest Pain.
Herman E. Hilleboe, Albany, N. Y., Public Health and Civil Defense.
Franz J. Ingelfinger, Boston, Benign Gastrointestinal Conditions.
Thomas M. Durant, Philadelphia, Dietary Factors in Arteriosclerosis.
Howard M. McCue Jr., Richmond, Va., Control of Rheumatic Heart Disease.

U.S.P. XIV Supplement.—A copy of the third United States Pharmacopeia XIV Supplement will be mailed to every registered holder of U.S.P. XIV, according to Lloyd C. Miller, Ph.D., director of Pharmacopeial Revision. Registry is effected by returning the card bound into the back of U.S.P. XIV. This automatically assures receiving a copy of every supplement issued, at no charge. As yet cards have not been returned for several thousand of the copies of U.S.P. XIV known to be in circulation. Considerable effort is being made to draw attention to the obligations of each owner in regard to returning the card and to keeping the U.S.P. office advised of any change in address. All presently registered holders of U.S.P. XIV should have received their copies of the supplement during August. This allows time for study and for making changes to comply with the new regulations before they go into effect on Jan. 1, 1952.

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Dietetic Association Meeting.—The American Dietetic Association will hold its annual meeting, Oct. 9-12 at the Public Auditorium in Cleveland. Approximately 4,000 dietitians, nutritionists, and guests are expected to attend. Some of the speakers scheduled to appear on the program and their topics include the following:

Fredrick J. Stare, Boston, Recent Advances in Nutrition.
George J. Hamwi, Columbus, Ohio, Studies in Geriatric Nutrition.
Howard B. Lewis, Ph.D., Ann Arbor, Mich., Fifty Years of Study of the Role of Protein in Nutrition.
Iago Galdston, New York, Nutrition from the Psychiatrist's Point of View.
Robert R. Williams, New York, Rice as a Factor in Asiatic Diets.
Dena Cederquist, Ph.D., East Lansing, Mich., Weight Reduction on a High Fat Diet.
Ralph D. Rabinovitch, Ann Arbor, Mich., Feeding to Meet Emotional Needs.

Other sessions will be devoted to institution management, professional education, and public health.

Maxillofacial Surgeons Meeting.—The annual meeting of the American Society of Maxillofacial Surgeons will be held at the Drake Hotel, Chicago, Sept. 23-26, under the presidency of Dr. John B. Erich, Rochester, Minn. Those speaking by invitation include the following:

Karl Meyer, Chicago, Primary Carcinoma of Neck.
James W. Hendrick, San Antonio, Texas, Head and Neck.
Eric Oldberg, Chicago, Cranial Complications of Facial Injuries.

There are three symposiums on the program: First, a symposium on cancer given Monday morning, the participants being Drs. George Milles, Irvin F. Hummon, and Eric M. Uhlmann, Chicago; Dr. John B. Erich, Rochester, Minn., and Dr. Hamilton A. Baxter, Montreal, Canada. The second symposium will be presented Tuesday afternoon on treatment of burns of the face. Participants will be Dr. Joseph G. Kostrubala, Chicago, and, by invitation, Drs. Derrick T. Vail and Louis Schultz, Chicago, and Dr. Clarence R. Straatsma, New York. The meeting will close Wednesday morning with a symposium on cleft palate and lip. Speakers will be Dr. Carl W. Waldron, Minneapolis; Dr. John W. Kemper, Ann Arbor, Mich.; Dr. Fred S. Dunn, New York; and, by invitation, Dr. Edward A. Kitlowski, Baltimore.

Parents' Guide to Cerebral Palsy.—How parents of children with cerebral palsy can help in developing services for these children is one of the important activities described in the new 76-page "Parents' Study Guide" published in July by the National Society for Crippled Children and Adults. The booklet was prepared in answer to many requests for help in forming a parents' group, planning a program for parent study, and assisting in building programs for children. The Program Study Outlines for 19 meetings cover specific phases of treatment, training, education, counseling, and other areas of interest with accompanying lesson outlines and source materials. The role of parents as members of the cerebral palsy team, and the projects they can assist in carrying on, are also listed. A bibliography of pamphlets, magazines, and books for parents of handicapped children and a listing of organizations which publish and distribute literature for child care and guidance and family living are included. In addition to professional guidance in preparing the booklet, the national society also received assistance from members of the National Cerebral Palsy Parents' Advisory Council. Because part of the publishing costs were defrayed through a grant, special prices on the booklet are being offered. For one to 25 copies, the cost is 50 cents each; 26 to 100 copies, 45 cents each; and more than 100 copies, 40 cents each. Copies are available from the National Society for Crippled Children and Adults, 11 S. LaSalle St., Chicago 3.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States in the weeks ended as indicated:

Area	Sept. 1, 1951	Aug. 25, 1951	Sept. 2, 1950
New England States			
Maine	4	4	3
New Hampshire	2	3	..
Vermont	..	5	1
Massachusetts	13	21	33
Rhode Island	..	3	5
Connecticut	34	20	32
Middle Atlantic States			
New York	119	109	286
New Jersey	45	32	34
Pennsylvania	54	46	49
East North Central States			
Ohio	74	83	98
Indiana	18	27	18
Illinois	128	90	122
Michigan	98	85	114
Wisconsin	104	107	55
West North Central States			
Minnesota	35	43	27
Iowa	33	38	95
Missouri	64	55	16
North Dakota	5	7	1
South Dakota	14	4	7
Nebraska	37	32	16
Kansas	52	63	24
South Atlantic States			
Delaware	1	..	3
Maryland	16	5	37
District of Columbia	6	14	15
Virginia	19	10	48
West Virginia	19	12	9
North Carolina	21	15	49
South Carolina	7	11	17
Georgia	36	47	14
Florida	9	13	17
East South Central States			
Kentucky	20	31	28
Tennessee	56	36	23
Alabama	24	54	8
Mississippi	31	56	18
West South Central States			
Arkansas	33	36	15
Louisiana	27	39	16
Oklahoma	27	34	19
Texas	70	84	102
Mountain States			
Montana	11	6	3
Idaho	7	7	8
Wyoming	5	15	..
Colorado	90	114	7
New Mexico	9	14	5
Arizona	36	25	11
Utah	39	53	..
Nevada	..	1	..
Pacific States			
Washington	23	17	41
Oregon	19	11	16
California	148	133	65
Territories and Possessions			
Alaska	4	1	..
Hawaii	..	..	..
United States	1,746	1,771	1,625

DEATHS IN OTHER COUNTRIES

Dr. George Grey Turner, emeritus professor of surgery at the universities of Durham and London, died in London Aug. 24, aged 73. He was a member of the council of the Royal College of Surgeons of England from 1926 to 1950. In 1949 he presided over the 13th congress of the International Society of Surgeons in New Orleans. Among the notable lectures he had given in this country were his oration at the clinical congress of the American College of Surgeons in Philadelphia in 1930; his Prosser White Oration in 1939; the George Halliburton Hume Memorial Lectures in 1943, and in 1949 the Moynihan Memorial Lecture. Among his publications are "Injuries and Diseases of the Oesophagus." In addition, he wrote several treatises on cancer.

MEETINGS

AMBULATORY FRACTURE ASSOCIATION, Arrowhead Springs Hotel, San Bernardino, Calif., Oct. 8-11. Dr. H. W. Wellmerling, 626 Griesheim Bldg., Bloomington, Ill., Secretary.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, Chicago, Oct. 14-18. Dr. W. L. Benedict, 100 First Avenue Bldg., Rochester, Minn., Executive Secretary.

AMERICAN ACADEMY OF PEDIATRICS, Toronto, Canada, Oct. 20-25. Dr. E. H. Christopherson, 636 Church St., Evanston, Ill., Executive Secretary.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA, The Seigniory, Montebello, Quebec, Canada, Oct. 23-25. Dr. Charles G. Johnston, 1512 St. Antoine St., Detroit 26, Secretary.

AMERICAN ASSOCIATION OF BLOOD BANKS, Hotel Nicollet, Minneapolis, Oct. 22-24. Miss Marjorie Saunders, 3301 Junius St., Dallas 1, Texas, Secretary.

AMERICAN CANCER SOCIETY, New York, Oct. 25. Dr. Charles S. Cameron, 47 Beaver St., New York, Medical Director.

AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION, Skytop, Pa., Nov. 5-7. Dr. Marshall N. Fulton, 124 Waterman St., Providence, R. I., Secretary.

AMERICAN COLLEGE OF SURGEONS, Fairmont Hotel, San Francisco, Nov. 5-9. Dr. Michael L. Mason, 40 E. Erie St., Chicago 11, Secretary.

AMERICAN HOSPITAL ASSOCIATION, St. Louis, Sept. 17-20. Mr. George Bugbee, 18 E. Division St., Chicago 10, Executive Director.

AMERICAN MEDICAL WRITERS' ASSOCIATION, Pere Marquette Hotel, Peoria, Ill., Sept. 19. Dr. Harold Swanberg, 209 W.C.U. Bldg., Quincy, Ill., Secretary.

AMERICAN PUBLIC HEALTH ASSOCIATION, Civic Auditorium, San Francisco, Oct. 29-Nov. 2. Dr. Reginald M. Atwater, 1790 Broadway, New York 19, Executive Secretary.

AMERICAN ROENTGEN RAY SOCIETY, Washington, D. C., Sept. 25-28. Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Secretary.

AMERCAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS, Chicago, Nov. 4-5. Dr. O. J. Pollak, Quincy City Hospital, Quincy 69, Mass., Secretary.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS, Washington, D. C., Nov. 5-8. Dr. J. Earl Remlinger Jr., 188 W. Randolph St., Room 909, Chicago 1, Secretary.

AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS, Chicago, Oct. 15-20. Dr. Clyde G. Culbertson, 1040 W. Michigan St., Indianapolis 7, Secretary.

AMERICAN SOCIETY OF MAXILLOFACIAL SURGEONS, Drake Hotel, Chicago, Sept. 23-26. Dr. Casper M. Epsteen, 25 E. Washington St., Chicago 2, Secretary.

ASSOCIATION OF AMERICAN MEDICAL COLLEGES, French Lick Springs Hotel, French Lick, Ind., Oct. 29-31. Dr. Dean F. Smiley, 185 N. Wabash Ave., Chicago 1, Secretary.

ASSOCIATION OF LIFE INSURANCE MEDICAL DIRECTORS OF AMERICA, New York, Oct. 11-12. Dr. Henry B. Kirkland, P. O. Box 594, Newark 1, N. J., Secretary.

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES, Palmer House, Chicago, Oct. 8-10. Colonel James M. Phalen, Armed Forces Institute of Pathology, Washington 25, D. C., Secretary.

CENTRAL NEUROPSYCHIATRIC ASSOCIATION, Hotel Nicollet, Minneapolis, Oct. 19-20. Dr. Lee M. Eaton, 102 Second Ave. S.W., Rochester, Minn., Secretary.

CENTRAL SOCIETY FOR CLINICAL RESEARCH, Drake Hotel, Chicago, Nov. 2-3. Dr. Kenneth G. Kohlstaedt, 960 Locke St., Indianapolis 7, Secretary.

COLLEGE OF AMERICAN PATHOLOGISTS, Chicago, Oct. 15-16. Dr. Tracy B. Mallory, Massachusetts General Hospital, Boston, Secretary.

COLORADO STATE MEDICAL SOCIETY, Denver, Sept. 18-21. Mr. Harvey T. Sethman, 1612 Tremont Place, Denver 2, Executive Secretary.

DELAWARE, MEDICAL SOCIETY OF, Wilmington, Oct. 8-10. Dr. Andrew H. Gehret, 1007 Park Place, Wilmington, Secretary.

DISTRICT OF COLUMBIA, MEDICAL SOCIETY OF THE, Hotel Statler, Washington, Oct. 1-3. Mr. Theodore Wiprud, 1718 M St. N.W., Washington, Secretary.

GULF COAST CLINICAL SOCIETY, Edgewater Gulf Hotel, Edgewater Park, Miss., Oct. 18-19. Dr. C. D. Taylor, 113 Davis Ave., Pass Christian, Miss., Secretary.

INDIANA STATE MEDICAL ASSOCIATION, Indianapolis, Oct. 29-31. Miss Lucille Kribs, 23 E. Ohio St., Indianapolis 4, Acting Secretary.

INTERSTATE POST GRADUATE MEDICAL ASSOCIATION OF NORTH AMERICA, St. Louis, Oct. 22-26. Dr. Tom B. Throckmorton, Equitable Bldg., Des Moines, Iowa, Secretary.

KANSAS CITY SOUTHWEST CLINICAL SOCIETY, Municipal Auditorium, Kansas City, Mo., Oct. 1-4. Dr. Maxwell G. Berry, 630 Shukert Bldg., Kansas City, Mo., Director of Clinics.

KENTUCKY STATE MEDICAL ASSOCIATION, Columbian Auditorium, Louisville, Oct. 2-5. Dr. Bruce Underwood, 620 S. Third St., Louisville 2, Secretary.

MICHIGAN STATE MEDICAL SOCIETY, Grand Rapids, Sept. 26-28. Dr. L. Fernald Foster, 606 Townsend St., Lansing 15, Secretary.

MIDWEST REGIONAL MEETING AMERICAN COLLEGE OF PHYSICIANS, Columbus, Ohio, Oct. 13. Dr. B. K. Wiseman, Kinsman Hall, Ohio State University, Columbus 10, Ohio, Chairman.

MISSISSIPPI VALLEY MEDICAL SOCIETY, Peoria, Ill., Sept. 19-21. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

NASHVILLE POSTGRADUATE MEDICAL ASSEMBLY, Maxwell House, Nashville, Tenn., Oct. 3-5. Dr. W. G. Kennon Jr., 647 Doctors Bldg., Nashville 3, Secretary.

NEW HAMPSHIRE MEDICAL SOCIETY, Equinox House, Manchester, Vermont, Sept. 30-Oct. 2. Dr. Deering G. Smith, 44 Chester St., Nashua, Secretary.

NORTH TEXAS-SOUTHERN OKLAHOMA FALL CLINICAL CONFERENCE, Wichita Falls, Texas, Sept. 19. Dr. W. L. Powers, 517 Hamilton Bldg., Wichita Falls, Chairman.

OKLAHOMA CITY CLINICAL SOCIETY, Biltmore Hotel, Oklahoma City, Oct. 29-Nov. 1. Mrs. Muriel R. Waller, 612 Medical Arts Bldg., Oklahoma City, Executive Secretary.

OMAHA MID-WEST CLINICAL SOCIETY, Hotel Paxton, Omaha, Oct. 29-Nov. 2. Dr. L. E. Moon, 1031 Medical Arts Bldg., Omaha 2, Secretary.

OREGON STATE MEDICAL SOCIETY, Masonic Temple, Portland, Oct. 10-13. Dr. Robert F. Miller, 833 S.W. Eleventh Ave., Portland 5, Secretary.

PENNSYLVANIA, MEDICAL SOCIETY OF THE STATE OF, Pittsburgh, Sept. 16-20. Dr. Walter F. Donaldson, 500 Penn Ave., Pittsburgh 22, Secretary.

SOUTHERN MEDICAL ASSOCIATION, Dallas, Texas, Nov. 5-8. Mr. C. P. Loranz, 1020 Empire Bldg., Birmingham 3, Ala., Secretary.

SOUTHWESTERN MEDICAL ASSOCIATION, El Paso, Texas, Oct. 18-20. Dr. W. W. Schuessler, 1415 First National Bank Bldg., El Paso, Texas, Secretary.

SOUTHWESTERN SURGICAL CONGRESS, Hotel Jefferson, St. Louis, Sept. 24-26. Dr. C. R. Rountree, 1227 Classen St., Oklahoma City 3, Secretary.

VERMONT STATE MEDICAL SOCIETY, Equinox House, Manchester, Sept. 30-Oct. 2. Dr. James P. Hammond, 542 Main St., Bennington, Secretary.

VIRGINIA, MEDICAL SOCIETY OF, Virginia Beach, Oct. 7-10. Mr. Richard H. Nash, 1105 W. Franklin St., Richmond, Executive Secretary.

WISCONSIN, STATE MEDICAL SOCIETY OF, Hotel Schroeder and Milwaukee Auditorium, Milwaukee, Oct. 1-3. Mr. Charles H. Crownhart, 704 E. Gorham St., Madison 3, Secretary.

WYOMING STATE MEDICAL SOCIETY, Rock Springs, Sept. 27-29. Dr. Glenn W. Koford, 2020 Carey Ave., Cheyenne, Secretary.

INTERNATIONAL

COMMONWEALTH AND EMPIRE HEALTH AND TUBERCULOSIS CONFERENCE, Central Hall, London, England, July 8-13. Dr. J. H. Harley Williams, Tavistock House North, Tavistock Sq., London, W.C.1, England, Secretary General.

EUROPEAN CONGRESS OF HEMATOLOGY, Rome, Italy, Oct. 3-6. Dr. Sven Moeschlin, Mediz Klinak, Zurich, Switzerland, General Secretary.

EUROPEAN CONGRESS ON RHEUMATISM, Barcelona, Spain, Sept. 24-27. Dr. Gunnar Edström, Lund, Sweden, Secretary.

INTER-AMERICAN CONGRESS OF SURGERY, Buenos Aires, Argentina, Oct. 1-6.

INTERNATIONAL ASSOCIATION OF ALLERGISTS, Zurich, Switzerland, Sept. 23-29. Prof. A. S. Grumbach, Hygiene Institut der Universitaet Zurich, Gloriastr. 32, Zurich, Switzerland.

INTERNATIONAL CONGRESS OF ANESTHESIOLOGY, Nursing School of the Salpiettre, 47 Boul de l'Hospital, Paris, France, Sept 20-22. 12 rue de Seine, Paris 6e, France, Secretariat.

INTERNATIONAL CONGRESS ON MENTAL HEALTH, Mexico City, Mexico, Dec. 11-19. Mrs. Grace E. O'Neill, Division of World Affairs, National Association on Mental Health, 1790 Broadway, New York 19, N. Y.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, London, England, July 14-19. Dr. A. C. Boyle, 45, Lincoln's Inn Fields, London, W.C.2, England, Hon. Secretary.

INTERNATIONAL SOCIETY OF SURGERY, Paris, France, Sept. 24-29. Dr. L. Dejardin, 141, rue Belliard, Brussels, Belgium, Secretary General.

PAN AMERICAN CONGRESS OF OPHTHALMOLOGY, Mexico City, Mexico, Jan. 6-12. Dr. Luis Sanchez Bulnes, Gomez Farias 19, Mexico 4, D.F., Secretary-General.

PAN AMERICAN CONGRESS OF PEDIATRICS, Montevideo, Uruguay, Dec. 5-8. Dr. Maria Luisa Saldien de Rodriguez, Avenida 18 de Julio, 1246, Montevideo, Uruguay, General Secretary.

PAN PACIFIC SURGICAL ASSOCIATION CONGRESS, Honolulu, Hawaii, Nov. 7-19. Dr. Forrest J. Pinkerton, Suite 7, Young Bldg., Honolulu, Hawaii, President.

WORLD MEDICAL ASSOCIATION, Stockholm, Sweden, Sept. 15-21. Dr. Louis H. Bauer, 2 E. 103d St., New York 29, N. Y., U. S. A., Secretary General.

EXAMINATIONS AND LICENSURE

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 24-26, 1952. Sec., Dr. D. G. Gill, 537 Dexter Ave., Montgomery 4.

ARKANSAS:* *Regular.* Little Rock, Nov. 8-9. Sec., Dr. Joe Verser, Harrisburg.

COLORADO:* *Reciprocity.* Denver, Oct. 9. Final date for filing application is Sept. 24. Ex. Sec., Mrs. Beulah H. Hudgens, 831 Republic Bldg., Denver 2.

GEORGIA: Atlanta, June. August, Oct. 9-11. Sec., Mr. R. C. Coleman, 111 State Capitol, Atlanta.

GUAM: The Commission on Licensure will meet whenever a candidate appears or submits his credentials. Ex. Sec., Dr. John Y. Battenfield, Agana.

ILLINOIS: Chicago, Oct. 9-11. Superintendent of Registration, Mr. Charles F. Kervin, Capitol Building, Springfield.

INDIANA: Indianapolis, June 1952. Sec., Dr. Paul R. Tindall, 1138 K of P Bldg., Indianapolis 4.

KANSAS: Topeka, Dec. 12-13. Sec., Dr. O. W. Davidson, 772 New Brotherhood Bldg., Kansas City.

KENTUCKY: *Examination.* Louisville, Dec. 11-13. Sec., Dr. Bruce Underwood, 620 S. 3rd St., Louisville.

MARYLAND: *Examination.* Baltimore, Dec. 11-14. Sec., Dr. Lewis P. Gundry, 1215 Cathedral St., Baltimore.

MICHIGAN:* *Examination.* Lansing, Oct. 10-12. Sec., Dr. J. Earl McIntyre, 202-4 Hollister Bldg., Lansing.

MINNESOTA: * Minneapolis, Oct. 16-18. Sec., Dr. Julian F. DuBois, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: *Reciprocity.* Jackson, December. Asst. Sec., Dr. R. N. Whitfield, Old Capitol Bldg., Jackson.

MISSOURI: *Examination.* Kansas City, Oct. 18-20. *Reciprocity.* Oct. 17. Exec. Sec., Mr. John A. Hailey, State Capitol Bldg., Jefferson City.

NEW JERSEY: *Examination.* Trenton, Oct. 16-19. Sec., Dr. E. S. Hallinger, 28 W. State St., Trenton.

NEW MEXICO:* Santa Fe, Oct. 8-9. Sec., Dr. Charles J. McGoey, Coronado Bldg., Santa Fe.

NEW YORK: *Examination.* Albany, Buffalo, New York and Syracuse, Oct. 31-Nov. 3. Sec., Dr. Jacob L. Lochner, Jr., 23 S. Pearl St., Albany.

NORTH CAROLINA: *Examination.* Asheville, Oct. 7-8. *Reciprocity.* Asheville, Oct. 8. Sec., Dr. Joseph J. Combs, Professional Bldg., Raleigh.

OHIO: *Examination.* Columbus, December. *Reciprocity.* Columbus, Oct. 2. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus 15.

OREGON:* *Reciprocity.* Portland, Oct. 12-13. *Examination.* Portland, Jan. 1952. Ex. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

SOUTH CAROLINA: *Reciprocity.* Columbia, Oct. 1. Sec., Dr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination.* Sioux Falls, Jan. 15-16. Ex. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

VIRGIN ISLANDS: Charlotte Amalie, Nov. 7-8. Sec., Dr. Earle M. Rice, St. Thomas.

WYOMING: *Examination.* Cheyenne, Oct. 1. Sec., Dr. Franklin D. Yoder, State Capitol, Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

CONNECTICUT: *Examination.* New Haven, Oct. 13. Exec. Asst., Miss Mary G. Reynolds, State Board of Healing Arts, 110 Whitney Avenue, New Haven 10.

DISTRICT OF COLUMBIA: *Examination.* Washington, Oct. 22-23. Sec., Dr. Daniel L. Seckinger, 4130 E. Municipal Bldg., Washington.

FLORIDA: Gainesville, Nov. 10. Sec., Mr. M. W. Emmel, Box 340, University of Florida, Gainesville.

MICHIGAN: Detroit and Ann Arbor, Oct. 12-13. *Examination.* Sec., Miss Eloise LeBeau, 501 W. Michigan Ave., Lansing 15.

MINNESOTA: *Examination.* Minneapolis, Oct. 2-3. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis.

NEBRASKA: *Examination.* Omaha, Oct. 2-3. Director, Bureau of Examining Boards, Mr. Oscar F. Humble, Room 1009, State Capitol Bldg., Lincoln 9.

OREGON: *Examination.* Portland, Dec. 1. Sec., Dr. Charles D. Byrne, State Board of Higher Education, University of Oregon, Eugene.

SOUTH DAKOTA: *Examination.* Vermillion, Dec. 7-8. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

TEXAS: *Examination.* Austin, Oct. 19-20. Chief Clerk, Mr. B. H. Kirk, 306 Nalle Bldg., Austin.

* Basic Science Certificate required.

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DEATHS

Sloan, Ruell Allen ✙ Washington, D. C.; born in Hartford, Conn., July 31, 1908; University of Rochester School of Medicine and Dentistry, Rochester, N. Y., 1935; specialist certified by the American Board of Pathology; secretary-treasurer of the American and Canadian sections of the International Association of Medical Museums; past vice president and president of the Washington Society of Pathologists; formerly secretary of the Pathological Society of the District of Columbia; member of the American Association of Pathologists and Bacteriologists, College of American Pathologists, and the American Society of Clinical Pathologists; assistant in pathology, 1937-1938, instructor in pathology, 1938-1939 and from 1941 to 1942 at Harvard Medical School in Boston; at one time instructor and acting assistant professor of pathology at St. Louis University School of Medicine, assistant professor of pathology, University of Buffalo School of Medicine; during World War II served as executive officer of the Army Institute of Pathology; formerly affiliated with Long Island and Children's hospitals in Boston, St. Mary's and Firmin Desloge hospitals in St. Louis, and the Edward J. Meyer Memorial Hospital in Buffalo; curator of the Medical Museum Department of the Armed Forces Institute of Pathology; died in his home in Chevy Chase, Md., June 17, aged 42.

Roper, Lonsdale Joseph ✙ Richmond, Va.; born in New York March 28, 1886; University College of Medicine, Richmond, 1907; since 1946 state health commissioner; in 1919 began his career in public health with the establishment of Portsmouth's first city health department; in 1937 became director of the venereal disease division of the state health department, and the next year was put in charge of the department's rural health division; specialist certified by the American Board of Preventive Medicine and Public Health; member of the Southern Medical Association and the Richmond Academy of Medicine; fellow of the American Public Health Association and past president of the State and Provincial Health Authorities of North America; served during World War I; at one time assistant professor of preventive medicine and public health at the Medical College of Virginia; died June 12, aged 65, of coronary thrombosis.

Martin, Harry Watson ✙ Los Angeles; born in Redfield, S. D., Jan. 18, 1890; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1912; husband of Columnist Louella O. Parsons; member of the American Urological Association; fellow of the American College of Surgeons; served during World War I and in the South Pacific during World War II; formerly served on the state athletic commission and the Los Angeles Board of Civil Service Commissioners; chief of the medical department at 20th Century Fox Studios; member of staff, California and Queen of Angels hospitals; senior urologist, Presbyterian Hospital-Olmstead Memorial, Los Angeles County Hospital, and Cedars of Lebanon Hospital, where he died June 24, aged 61, of lymphosarcoma.

Stone, Murray Chaffee ✙ Springfield, Mo.; born in Leominster, Mass., in 1880; Harvard Medical School, Boston, 1903; specialist certified by the American Board of Pathology; member of the College of American Pathologists and the American Society of Clinical Pathologists; past president of the Greene County Medical Society; sheriff and formerly county coroner; in 1912 and 1913 state bacteriologist for the state board of health; served during World War I; consultant for the Medical Center for Federal Prisoners; attending pathologist for the Veterans Administration Hospital; pathologist for the Springfield Baptist Hospital, City Hospital, and St. John's Hospital, where he died June 12, aged 71, of gastrointestinal hemorrhage.

Brown, Hubert Leslie ✙ Hinsdale, N. H.; Baltimore Medical College, 1903; affiliated with Memorial Hospital in Brattleboro and Elliot Community Hospital in Keene; died June 24, aged 76, of coronary thrombosis.

✙ Indicates Fellow of the American Medical Association.

Burden, Verne Gerard ✙ Philadelphia; University of Pennsylvania School of Medicine, Philadelphia, 1919; certified by the National Board of Medical Examiners; fellow of the American College of Surgeons; medical director of the Eastern State Penitentiary Hospital; chief of staff of Our Lady of Lourdes Hospital in Camden, N. J.; served on the staff of St. Joseph's Hospital; formerly fellow in surgery at the Mayo Foundation in Rochester, Minn.; died June 23, aged 56.

Burnett, Charles Borromeo, South River, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1893; died May 12, aged 79, of chronic myocarditis.

Gannon, Clarence Peter Lee, Kingston, N. Y.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1916; past president and for many years secretary of the Ulster County Medical Society; member of the Association of Military Surgeons of the United States; served during World War I; for many years health officer of the town of Ulster; affiliated with Kingston and Benedictine hospitals; died June 22, aged 67.

Gousse, William Louis ✙ Fairfield, Me.; Baltimore Medical College, 1911; past president of the Kennebec County Medical Association; served as school physician and health officer of the town of Fairfield; affiliated with Thayer Hospital and Sisters' Hospital in Waterville, where he died June 16, aged 73, of cerebral thrombosis, and diabetes mellitus.

Greenstein, Harry ✙ New York; University and Bellevue Hospital Medical College, New York, 1899; affiliated with New York Polyclinic Medical School and Hospital; died in Hunts Point Hospital May 25, aged 74.

Griffin, Fred, Mexico, Mo.; Washington University School of Medicine, St. Louis, 1904; member of the American Medical Association; past president of the school board; affiliated with Audrain Hospital; died June 20, aged 70, of heart disease.

Hayden, Louis Brooks ✙ Livermore Falls, Maine; Tufts College Medical School, Boston, 1897; an Associate Fellow of the American Medical Association; served during World War I; formerly school physician in Plymouth, Mass.; died June 12, aged 76, of pneumonia.

Jones, Frederick Goodwin ✙ Utica, N. Y.; Syracuse University College of Medicine, 1909; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; past president of the Utica Academy of Medicine; served overseas during World War I; affiliated with St. Luke's Home and Hospital, St. Elizabeth, Faxton, Utica State, and Masonic Soldiers and Sailors Memorial hospitals; died June 5, aged 67, of coronary occlusion.

Schneider, Harry ✙ New York; Boston University School of Medicine, 1922; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; on the staff of Beth Israel Hospital; died April 20, aged 54, of cerebral thrombosis.

Simmons, George W., Ripley, W. Va.; Maryland Medical College, Baltimore, 1903; for many years director of the bank of Ripley; died June 11, aged 72, of carcinoma.

Smullen, James Joseph Jr., Wisconsin Rapids, Wis.; Loyola University School of Medicine, Chicago, 1934; member of the American Medical Association; affiliated with Riverview Hospital; died June 12, aged 42, as the result of a fall.

Stone, Eustace B., Roanoke, Va.; Medical College of Virginia, Richmond, 1893; on the staff of Shenandoah Hospital; died April 17, aged 83, of coronary embolism.

Wood, James William, Hanceville, Ala.; Southern Medical College, Atlanta, 1897; died in Birmingham May 3, aged 78, of hypostatic pneumonia and arteriosclerosis.

GOVERNMENT SERVICES

AIR FORCE

Air Evacuation Units Trained to Use Respirators.—A course in the operation, maintenance, and theory of all types of portable respirators, believed one of the first of its kind offered in the field, is now being given to selected personnel of the 1453rd Medical Air Evacuation Squadron at Hickam Air Force Base, Oahu, T. H. Highly qualified instructors of the unit, using working models of the respirators and conventional iron lung, are instructing 12 airmen, eight hours a day, five days a week, in this specialized field. Each class lasts 30 days, and the training is so thorough that graduates know how to correct any mechanical failures that might occur. The project is supervised by Comdr. Karl R. Whitney, deputy surgeon of PACD, Military Air Transport Service.

Effective with victims of polio and spinal afflictions, the respirators can be used in either type C-54 or C-97 type aircraft of the 1500th Air Transport Wing now used in flying the Pacific airlift for MATS.

Medical officer demonstrates operation of portable respirator for use in planes of air evacuation units.

Aeromedical School Survey.—Almost 80% of the work done at the Air Force School of Aviation Medicine is devoted to research on the medical problems of flight, according to a survey made by Col. Frederick J. Frese Jr., deputy commandant of the school. A trifle more than 16% of the school's effort is required at present to train Air Force doctors in the special techniques of aviation medicine. A scant 4% of its energies are expended on the clinical practice of medicine. The survey findings cover only the activities of the aeromedical school headquarters at Randolph Field. Because of the heavy demand for more medical personnel in the Air Force, training of flight nurses and enlisted technicians was transferred last year to a branch of the school at Gunter Air Force Base in Alabama. The Gunter branch is reporting its manpower requirements separately. The results of the survey will be used to determine the size of the staff needed to operate the School of Aviation Medicine during the next academic year.

New Assignments.—Five officers left the Randolph Field School of Aviation Medicine Aug. 15 for permanent duty at other bases. Lieut. Col. David S. Evans, head of the department of neuropsychiatry since 1949, Capt. George W. Ell, assistant to the chief of the clinical medicine group since 1948, and Lieut. Paul B. Mullin, assistant in psychology, all received overseas assignments. Col. Ernest J. Cone was assigned to the Surgeon General's office in Washington, while Maj. Virgil R. Zarling goes to Maxwell Air Force Base, Alabama.

PUBLIC HEALTH SERVICE

Find Encephalitis Virus in Birds, Insects.—A research team of the Public Health Service's Communicable Disease Center has isolated the virus of encephalitis from wild birds under natural conditions, in a series of field tests in Weld County, Colo. The Laboratory work was performed at the Communicable Disease Center at Montgomery, Ala. "It has been suspected for many years that birds harbor the virus, but this is the first time that their role definitely has been proven," said Dr. T. Aidan Cockburn, epidemiologist in charge of encephalitis studies in the Office of Midwestern CDC services.

Isolation of the virus was reported twice from redwing blackbirds, and once from magpies, as well as from two batches of mosquitoes and one group of mites. Dr. Cockburn points out that wild birds, now proved to harbor the virus, do not become "sick" but act only as carriers, from which mosquitoes can acquire the virus. PHS figures show that the incidence of encephalitis in the United States increased in 1950 for the second straight year. In 1948 there were 575 reported cases; in 1949, 781 cases, and in 1950, 1,051 cases. Dr. Cockburn said the increase possibly was a result of better recognition of the disease. However, he further said, "Many thousands more are believed to have gone unrecognized or to have been erroneously diagnosed as poliomyelitis."

The Colorado State Department of Public Health and the Weld County Health Department cooperated in the research program. The public health team was comprised of a physician, an ornithologist, two entomologists, a nurse, a veterinarian, and virologist.

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Safe Milk Communities.—Fifty-four communities have been added to the list of safe milk communities, which is issued semiannually by the Public Health Service, and 21 communities on the previous list have been dropped. The new listing includes 211 cities and counties and is for the period of July 1949 to June 1951, inclusive. The ratings made by state milk sanitation authorities and reported to the Public Health Service are based on the Public Health Service Milk Ordinance which has been adopted by 369 counties and 1,492 municipalities in 39 states. A community must receive a rating of at least 90% for a two-year period by the state authority to be eligible for the "honor roll." The ratings are concerned with health of dairy cattle, sanitary methods of handling milk, proper cooling, and adequate pasteurization.

The semiannual list is published as a measure to encourage the maintenance of a high level of sanitation among communities which have adopted the Public Health Service Ordinance. A separate list is compiled for communities in which both raw and pasteurized milk are sold. No comparison is intended with communities operating under other milk ordinances. The current list appears in the Aug. 24, 1951, issue of *Public Health Reports*.

Civilian Health Requirements Officer.—Sanitary Engineer Director Wesley E. Gilbertson, executive officer of the Public Health Service's Communicable Disease Center at Atlanta, has been designated chief of the service's division of civilian health requirements. Mr. Gilbertson will be in charge of carrying out those claimant functions that have been assigned by the Defense Production Authority to the Federal Security Administrator and delegated by him to the Public Health Service. These relate to the construction requirements of hospitals and health centers and to supplies in the health field including those needed by hospitals, health departments, private practitioner clinical laboratories, and industrial clinics. Mr. Gilbertson will be assisted by Mr. Charles Lavin, also of the Communicable Disease Center, who has been coordinator of the program since its inception.

Grants.—The National Institute of Arthritis and Metabolic Diseases, established by Congress last year as one of the National Institutes of Health, has awarded 24 grants, totalling $314,465, to nonfederal medical scientists for special study in this field.

FOREIGN LETTERS

SPAIN

Congress of Spanish Cardiologists.—The third National Congress of the Spanish Society of Cardiology was held in Valencia, Dec. 5-8, 1950. Prof. Dr. F. Rodriguez Fornos, dean of the Faculty of Medicine of Valencia, was the president. Official topics were (1) treatment of cardiac insufficiency, (2) congenital heart diseases, and (3) unipolar leads in electrocardiography. Speakers on the first topic were Professors M. Beltran Baguena (Valencia) and T. Alday Redonnet (Madrid). Beltran Baguena reviewed the treatment of cardiac insufficiency. Drs. D. A. Gonzales Cruz, J. Baguena Candela, D. V. Sorribes, and D. V. Tormo, collaborators of Prof. Beltran Baguena, discussed the treatment of cardiac insufficiency. Dr. Baguena Candela reviewed surgical treatment of congestive cardiac insufficiency. Drs. E. Alcala Llorente and Martinez Ramon dealt with the more adequate treatment of geriatric cardiac insufficiency. The studies of Prof. Beltran Baguena and collaborators were based on clinical observations of 662 cases: in 426 cases of left cardiac insufficiency, 19 cases of right cardiac insufficiency, 211 cases of total cardiac insufficiency, and six cases of nonspecific heart disease, mainly cardiac neuroses.

Prof. T. Alday Redonnet has published some 40 papers based on his pharmacologic studies of digitalis in Spanish medical journals. He spoke about the clinical application of the drug on the basis of experimental results. The Hatcher-Magnus method of digitalis assay may yield grossly erroneous results. In 1927 he found that a Spanish digitalis containing 16 cat units per gram was practically inactive when administered to patients; however, these patients improved rapidly after administration of 1 mg. of digitoxin. He later assayed Digitalis lanata and found it very active. However, clinical results were poorer than results with the standard digitalis. On the other hand, when he assayed the Digitalis thapsi of Spain, he found that it was only slightly more active than Digitalis purpurea. However, when administered to patients, it was three or four times more active than Digitalis purpurea.

In 1933, he submitted an extensive report on the subject to the Committee of Biologic Standardization of Drugs of the League of Nations. In the report he called the attention of the committee to the unreliability of this method. However, the report was not published by the committee. In 1932, he suggested a method of bioassay of digitalis that should give results applicable to the clinical administration of the drug. He maintained that methods in which frogs, rabbits, guinea pigs, and pigeons are used are of no value. Only the methods in which cats and dogs are used are reliable, provided that the drug is given to the animals by the same route of administration as that used clinically. The cumulative power of the drug must also be borne in mind.

Prof. Alday Redonnet described the activity of 58 glycosides and genins, as measured either by the Hatcher-Magnus method or by his own method. Of the galenical preparations, digitalis injection is of very low activity. Preparations of Adonis vernalis, scilla, and several types of strophanthus are of low activity when administered by mouth. However, when given intravenously they have effects similar to those obtained with digitoxin and with intravenous use of lanatoside C. Digitalin and digitoxin are of value when administered orally, since they are almost completely absorbed by the intestine. Digitoxin is more active when it is injected slowly than when it is injected rapidly. Convallatoxin, ouabain, and oleandrin do not increase in toxicity when they are injected slowly.

The speaker discussed the various hypotheses concerning the mechanism of action of digitalis on circulation. The toxicity of glycosides containing sulfhydryl groups does not diminish when those compounds are given either in association with or after intravenous injection of dimercaprol (BAL).

Dr. A. Lamelas, head of the department of cardiology and endocrinology of the Casa de Salud Valdecilla (Santander), spoke on congenital heart disease. He reviewed the embryology, classification of congenital heart disease, and the general methods of diagnosis, with special reference to intracardiac catheterization, angiocardiography, and electrocardiography. He discussed the frequency and etiology of congenital heart diseases and reviewed 130 necropsies. Common pathologic features of congenital heart disease are bacterial endarteritis or endocarditis, imperfect physical development, tuberculosis, and congenital abnormalities. Dr. Lamelas discussed, also, cyanosis and anoxemia and the possibility of sudden death.

Dr. A. Duque Sampayo (Madrid), head of the department of cardiology of the Institute of Medical Pathology, of which Dr. Maranon is director, spoke on unipolar leads in electrocardiography. Classic bipolar leads give information only of the changes of position of the heart in relation to the anteroposterior axis, whereas the unipolar leads from the extremities and Wilson's precordial leads give complete account of the changes of position of the heart in relation to its three axes. Unipolar leads are confirmatory in the diagnosis of ventricular hypertrophy, since they give clear electrocardiographic data, showing especially the increased time of the intrinsic deflection. Standard leads do not give diagnostic data in 50% of the cases of myocardial infarct. Unipolar leads have clarified greatly the problems of bundle branch block. They show the origin of extrasystoles and may eventually clarify the problem of complete arrhythmia.

BRAZIL

Curative Action of Chloramphenicol and Dihydrostreptomycin in Frambesia Tropica.—Dr. F. Nery Guimarães of the Oswaldo Cruz Institute reported the results of the treatment of yaws (frambesia tropica) with chloramphenicol and dihydrostreptomycin (five and four cases, respectively). Chloramphenicol was administered orally for 10 days with a total of 10 gm. in four cases and 20 gm. in one case. The daily total was divided into two doses. The period of treatment with dihydrostreptomycin was also 10 days, with a total of 10 gm. divided into 20 intramuscular injections. The results were reported together, for the two groups, as they were comparable. Clinical cure was obtained between 10 and 20 days from the beginning of treatment. Spirochetes were usually no longer present 48 hours after the beginning of treatment; however, in one case, the organisms were present even after 72 hours. A positive serologic reaction was reported in four cases (two in each group) immediately after the beginning of treatment, but in all cases the results changed to completely negative. The authors are entirely satisfied with the first results of treatment.

Early Diagnosis of Pregnancy and Heterogenetic Reactions with Proteus OX19.—The frequency of a positive agglutination test with the strain Proteus OX19 in serums of normal and nonpregnant women led Dr. Maria I. Mello, of the Oswaldo Cruz Instituto, to investigate the influence of the blood groups on this reaction. As the specific substance in the chemical composition of blood group A is closely related to that of gonadotropic hormones and of Proteus OX19, it might be possible to find some correlation between blood group and Proteus OX19 agglutination. The results of the investigation disclosed that Proteus OX19 agglutinates only with blood group A serum, the highest agglutination titer being 1: 80, while with the serum of pregnant women the titers are in almost all cases higher than this. An attempt is being made to perform the test with the isolated polysaccharides instead of the 24-hour Proteus OX19 culture. In cases of suspected pregnancy with a low agglutination titer, it is necessary that one know the blood group to assure the value of the agglutination test for diagnosis. Normal serums belonging to the other blood groups gave negative results under Dr. Mello's experimental conditions.

The items in these letters are contributed by regular correspondents in the various foreign countries.

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CORRESPONDENCE

ORTHOPEDICS AND INDUSTRY

To the Editor:—The article by Dr. Billig relating to Industrial Orthopedics, published in THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, July 28, 1951, should not be allowed to pass without comment and question. The article, if accepted as representative of modern American orthopedics, would indicate that most advances in our specialty in recent years have been wrongly conceived and ill-advised.

Dr. Billig, by insinuation at least, classifies every physical complaint of the man in industry as due to some postural soft tissue abnormality which can be miraculously corrected by a few simple exercises performed three times daily. He does not even mention the many possible etiological factors which must be considered in the differential diagnosis of these problems. Any industrial concern which blindly follows such a program will force many of its employees to seek medical care outside of their own facilities for relief of those symptoms which arise from true organic lesions. In fact, the majority of complaints which could be satisfactorily managed with the regimens described by Dr. Billig would undoubtedly be functional in character.

I think it should be clearly stated that the opinions expressed by Dr. Billig may not represent the attitude of the average orthopedic surgeon toward the problem of medical care in industry.

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To the Editor:—In THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, July 28, 1951, page 1179, there appeared an article by Dr. Harvey E. Billig Jr., of Los Angeles, entitled "The Specialist Looks at Everyday Medical Care in Industry: Orthopedics." In this he states: "Chronic posture habit results in shortening of the fascial ligamentous fibrous structures to accommodate the posture maintained. When this is occupational, and when the occupational posture habit becomes the chronic posture habit, the gradually ensuing contractural stiffness results in not only a poor posture habit but symptoms as well. The management of a telephone company noticed a huge prevalence of backache, dysmenorrhea, and occipitocervical headaches radiating to the temporal region among the thousands of girls seated with forward thrust of head and neck at switchboards. Examination revealed a contracture of the ligaments in the cervical region and in the lower back region, radiating to the anterior pelvis, thence to the leg and iliotibial-band attachment at the lateral condyle of the tibia. In these girls the forward thrust of head and neck and the forward-tilted pelvis had thus become a fixed posture habit. Placing an additional pull on the contracted ligaments in the neck by means of forced craniocervical rotation exacerbated the headache radiating up over the head into the peripheral distribution of the greater and lesser occipital nerves. After mobilization of this contracture by means of progressive accumulative loosening through forced cervical-rotation stretching exercises done routinely three times to each side three periods daily, the headaches cleared up, not to return. Likewise, placing an additional pull on the ligaments running from the dorsolumbar portion of the back to the anterior pelvis, thence to the leg, exacerbated the symptoms of backache and menstrual cramps (pain radiating into the peripheral distribution of the ilioinguinal and iliohypogastric nerves arising from the twelfth dorsal and first lumbar nerves passing through the contracted fascial ramifications). After mobilization of the contracture by means of the progressive accumulative loosening through forced posterior tilt of back and pelvis on the leg done routinely three times to each side three periods daily, the backache and menstrual cramps cleared up, not to return. These 'stretching exercises' are now a part of the employee health service program of American Telephone and Telegraph Company and are illustrated by diagrams in a booklet distributed to all its employees."

The background for a portion of the above references is probably as follows: In an article entitled "Menstrual Exercises" (*Indust. Med.* **12**:588 [Sept.] 1943) Dr. Billig postulated that dysmenorrhea was frequently the result of "a postural defect of contracted fascial ligamentous bands restricting posterior tilt excursion range of the pelvis in relation to the legs and back. At menstruation (with the change in ovarian hormone level) the ligaments further shorten causing impingement with irritation of the peripheral spinal nerves passing through and by them. The nerves usually irritated are one or more of the following: the 11th dorsal, the 12th dorsal, the first lumbar and their branches, the ilioinguinal and iliohypogastric. The impingement gives rise to symptoms of pain in the low back in the region of irritation or in the region of distribution of these nerves in the lower abdominal wall or groin or both."

This article was co-authored by Dr. A. C. Dick, then medical director of the Consolidated Vultee Aircraft Corporation, and Mrs. H. N. Macy, chief nurse of the same corporation. It was reported that they had achieved a most remarkable decrease absenteeism, reduction in the use of menstrual cramps as an absentee excuse and increased efficiency as a result of the use of the Billig exercises for dysmenorrhea.

Parenthetically in "Queries and Minor Notes" in THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (March 17, 1945, page 684), in commenting upon this theory it was stated: "It has not been proved that in all or most women with primary dysmenorrhea 'there is a postural defect of contracted fascial ligamentous bands restricting posterior tilt excursion range. . . .' Likewise there is no proof that at menstruation the ligaments further shorten, impinge and irritate the peripheral spinal nerves enumerated in the query. . . . In view of the favorable results described, if there was not a large psychic factor involved, some other reason for the benefits must be sought than that given by the proponents."

It should also be noted that the Billig exercises were being taught to the girls in the public schools of Los Angeles in 1944. These factors contributed to an interest by some of the women employees of the Pacific Telephone and Telegraph Company in Los Angeles. On Oct. 11, 1944, the first groups of women in the accounting department were trained in the exercise by a psychotherapist from the Harlan Shoemaker Foundation in Los Angeles, an organization which was sponsoring this activity. The accounting department first introduced the program, then the plant department used the plan, the latter part of October, 1944, and the traffic and commercial department commenced the program in November. Attendance was on a voluntary basis, and all women were given the opportunity to attend if they so desired. The group instructions took approximately three-quarters of an hour, and a case history on each of the girls was taken before proceeding. Subsequent reports made to Dr. Jerome Shilling, medical director of the telephone company in Los Angeles, by the managers of the respective departments in the spring of 1945, indicated that the program had been participated in by 424 plant women employees, 386 commercial women employees, 325 in the accounting department and one class of 62 traffic women employees. It should be noted that in the plant, commercial, and accounting departments the classes were given on company time and in the traffic department on employees' time. The initial enthusiasm apparently soon decreased, and the program has not been continued, largely owing to the disinclination of the women to persevere with the procedure. As expressed by Dr. Shilling, "Regular exercise three times a day becomes monotonous and the individuals are prone to 'drop by the wayside' from this standpoint." In a letter dated Feb. 4, 1946, Dr. Shilling stated: "In conclusion and in specific answer to questions included in your letter, our results have not been conclusive or favorable. I do believe that in very occasional, selected specific cases that definite benefits do result. All in all, however, it has not been our experience that absenteeism was materially affected during the period of time that a number of employees were given instructions at the Billig Clinic. It might be said that we have not given

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this matter a fair and sustained trial. However, as stated above, it is all but impossible to get an individual, male or female, to continue with exercises in the prescribed manner and frequency over any sustained period of time. Other than for dysmenorrhea, we have had little or no experience with the exercises given for other conditions. . . . I have, however, had the opportunity to observe cases treated from other organizations and I am yet to be convinced this procedure is the answer to these perplexing chronic problems."

In June, 1945, at a Bell System Medical Directors' Conference, the then existing reports on the Billig exercises and the contents of a brochure by Dr. Billig, "Thirty Days Hath September," which deals with menstruation, were discussed. In the notes of that conference we stated: "It has been our opinion that from an objective scientific viewpoint the available evidence on an anatomical and physiological basis leaves considerable to be desired in the way of explanation compared with the reported results. The question appears not to be whether or not the Billig exercises will stand in a cold light of scientific appraisal but rather whether or not there may be justification for including it as part of the information on this subject to be made available to our employees." The consensus was that the exercise was not harmful, and it was included with three other exercises as suggestions for possible relief in dysmenorrhea. This booklet is not distributed to all employees as was stated in Dr. Billig's July 28, 1951, article but rather has been used in conjunction with health education group discussions and in the various company medical departments in specific individual situations.

It is contended that the statement "The management of a telephone company noticed a huge prevalence of backache, dysmenorrhea, and occipitocervical headaches radiating to the temporal region among the thousands of girls seated with forward thrust of head and neck at switchboards" is without basis in fact. It is also our opinion, based on the reports of many competent observations, that the incidence of the conditions referred to is no greater, if as great, among telephone operators as compared with any of the clerical groups. A great deal of research has been done in the development of switchboards and operators' chairs with the objective of comfort and good posture. The suggestion that backache, dysmenorrhea, and occipitocervical headaches are occupational in origin is also without basis in fact as related to the requirements of switchboard operating.

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ALKALOSIS AND HYPERVENTILATION

To the Editor:—In their article entitled, "Alkalosis Due to Hyperventilation" (*J. A. M. A.* **146:**1125 [July 21] 1951), Sattler, Marquardt, and Cummins stress the importance of pH determinations for determining the presence of respiratory alkalosis. They state that a review of the literature "reveals no clinical reports of hyperventilation alkalosis."

In their report they cite three cases where they feel the test was of diagnostic value. The first two appear to be well-confirmed cases of hyperventilation on a psychoneurotic basis; however, I question the conclusion that the pH determination aided in the diagnosis. In both cases the pH was within normal limits before a test period of voluntary hyperventilation. In the first case, the pH rose to 7.55 after 12 minutes of voluntary hyperventilation; in the second, it reached 7.49 after five minutes of hyperventilation. These values are well within normal physiological limits. In the third case, that of a patient with cardiac disease who at the time was definitely irrational, the pH was 7.62. Restoration of the pH to normal by the use of ammonium chloride was accompanied by disappearance of the mental confusion.

It is well known that cardiac disease is one of the causes of lowered alveolar carbon dioxide tension. In this case, apparently it was sufficient to produce decompensation of the acid-base balance with production of true alkalosis. The first two, however, may well have been cases of carbon dioxide deficit, but, since the pH was within normal limits (before the hyperventilation test period), they were definitely compensated. A test of the blood for bicarbonate level would have determined whether a carbon dioxide deficit was actually present.

As to the value of ventilation test periods in determining the presence of hyperventilation, attention is called to an article by Carryer (*Proc. Staff Meet.*, Mayo Clin. **22:**456 [Oct. 1] 1947) in which the reciprocal relationship of carbon dioxide and pH of the serum during hyperventilation is portrayed in a chart. A quick swing to a very high level of pH accompanies voluntary hyperventilation even under completely physiological conditions. A further rather extensive discussion of the subject, with some results of experimental observation, appears in an article by me (*Postgrad. Med.* **7:**85 [Feb.] 1950).

I agree that determination of the pH of the serum is valuable in these cases; however, in order to determine precisely the patient's condition at any one time, a bicarbonate level of the blood should be part of the procedure.

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ACTH, CORTISONE, AND TUBERCULOSIS

To the Editor:—The Committee on Therapy of the American Trudeau Society asks the cooperation of the medical profession in a survey of the possible deleterious effects of cortisone and corticotropin (ACTH) on tuberculous infection in man. Experimental work has indicated this possibility, and scattered clinical experience has suggested that both compounds may have a harmful effect in human tuberculosis.

The American Trudeau Society, through its Committee on Therapy, is anxious to obtain information confirming or disproving this impression and asks the cooperation of physicians throughout the country in collecting pertinent data, as outlined below. Since tuberculosis is a common chronic disease, it seems likely that many physicians have had an opportunity to observe the effects of corticotropin or cortisone on tuberculous infection coincident with the treatment of other disease states. The Committee believes that this information is of sufficient importance to make such a study worth while; suitable material would provide information of considerable significance which otherwise might not be available for years.

It is understood, of course, that the Committee in no way wishes to interfere with the publication of results by individuals contributing to this study, and will respect any restrictions in the use of material.

Information is desired concerning both pulmonary and extrapulmonary tuberculosis, as to whether any clinician has observed any of the following effects: (1) no apparent effect in patients with known active tuberculosis, (2) an exacerbation of clinically active or apparently inactive tuberculosis during or after treatment with cortisone, or (3) a favorable effect in active tuberculosis.

If such cases are available, the following data would be greatly appreciated: (*a*) a brief clinical history, including a statement concerning the disease for which treatment was given, and whether or not active or inactive tuberculosis was suspected before treatment was begun; (*b*) pertinent laboratory data, including results of sputum examination for tubercle bacilli; and (*c*) the temporary loan of representative x-rays related to the tuberculosis, if available, before, during, and after treatment. This information should be sent to Dr. Robert H. Ebert, University of Chicago Clinics, 950 E. 59th St., Chicago 37.

William B. Tucker, M.D., Chairman,
Committee on Therapy, American Trudeau Society,
University of Minnesota, Minneapolis 14.

LUDVIG HEKTOEN

To the Editor:—In the long, honored, indeed magnificent career of Dr. Ludvig Hektoen to which you give praise in The Journal of July 14, 1951, we wish to note a service, overlooked in your obituary to him. Dr. Hektoen, in his wisdom and tolerance and foresight, became a member of the first Board of Trustees of the Institute for Psychoanalysis in 1932 and remained actively interested in the work of the Institute throughout his life. For us to overlook mention of this service would be wholly out of keeping with the gratitude and affection we bore to this great scientist.

Helen Ross, Administrative Director,
The Institute for Psychoanalysis, Chicago.

MEDICAL LITERATURE ABSTRACTS

UNITED STATES

A.M.A. Arch. Dermat. and Syphilol., Chicago

64:1-118 (July) 1951

Prognosis of Dermatitis Herpetiformis, Treated and Untreated. W. H. Eyster Jr. and R. R. Kierland.—p. 1.
Oral Administration of Procaine with Ascorbic Acid, with Special Reference to Therapy of Pruritus. H. Luddecke.—p. 9.
Antiquity of Syphilis with Some Observations on Its Treatment Through the Ages. H. N. Cole.—p. 12.
Melanin Pigmentation and Hepatic Disease. F. A. Whitlock.—p. 23.
Further Studies in Autoeczematization. B. M. Espiin and F. E. Cormia. —p. 31.
Erythroderma Ichthyosiforme Congenitum: Epidermotectoscopical Description of Case. A. Vukas.—p. 36.
*Treatment of Seborrheic Dermatitis with Shampoo Containing Selenium Disulfide. W. N. Slinger and D. M. Hubbard.—p. 41.
Streptomycin Therapy of Erythema Induratum. F. G. Witherspoon and C. M. Hamilton.—p. 49.
*Contact Dermatitis Due to Cinnamon: Recurrence of Dermatitis Following Oral Administration of Cinnamon Oil. W. Leifer.—p. 52.
Further Clinical Observations on Seabather's Eruption. S. L. Moschella. —p. 55.
Acrodermatitis Pustulosa Perstans: Method of Treatment. H. C. Fishman. —p. 56.
Granuloma Annulare: Dissemination Following Administration of Calciferol. H. H. Sawicky and N. B. Kanof.—p. 58.
Atrophia Maculosa Varioliformis Cutis. L. R. McCorriston and H. C. Roys.—p. 59.
Dystrophia Unguium Mediana Canaliformis. R. D. Sweet.—p. 61.
Genitocrural Pruritus from Oral Aureomycin. A. J. Reiches and P. K. Webb.—p. 63.
Impetigo Herpetiformis Treated with Aureomycin. C. Sheard.—p. 64.
Contact Dermatitis Caused by Bamboo. B. L. Schiff.—p. 66.

Selenium Disulfide in Seborrheic Dermatitis.—Sulfur compounds and preparations have been recommended for the therapy of a great variety of dermatoses, particularly for parasitic infestations and seborrheic dermatitis. In the search for more efficient substances in the topical treatment of the seborrheic dermatoses, selenium was considered for therapeutic trial, because of its general properties and the group relationship of sulfur and selenium. However, because selenium compounds had been known to have toxic effects, there was some hesitation about using them clinically. Some selenium compounds penetrate the intact skin, and many of the more stable inorganic compounds might be studied for possible therapeutic use. A moderately stable preparation of selenium disulfide was selected for this study, in the form of a shampoo, which contained 2.5% of selenium disulfide and 17% of sodium alkyl aryl sulfonate (nacconol®) a surface-active agent, besides inert and stabilizing agents and water. It was found by 48-hour and repeated patch tests for four weeks that the active constituent of the shampoo, selenium disulfide, produced neither primary irritation nor sensitization reactions in 10 normal subjects. The shampoo was employed therapeutically over periods from one to seven months in 104 cases, 90 of which were cases of seborrheic dermatitis, without inducing signs of irritation, sensitization, or toxicity. There was complete control of 81% of the cases of seborrheic dermatitis of all degrees of severity. The shampoo did not influence the clinical course of seven cases of tinea capitis associated with the presence of Microsporum audouini. In two patients with atopic dermatitis and three patients with exfoliative dermatitis the amount of scaling of the scalp was reduced. In 19 patients who used the selenium shampoo once on their diseased scalp no absorption of selenium was evidenced by an increase in the excretion of selenium in the urine. After the use of the shampoo on the badly fissured scalps of two patients for 14 and 19 successive days, respectively, there was no definite evidence of initial or progressive absorption of selenium.

Dermatitis Due to Cinnamon.—In the case reported in this paper, a chronic vesicular dermatitis of the hands of five years' duration was found to be due to tooth paste flavored with cinnamon oil. The hand eruption had occurred first and had apparently been induced by repeated contact with cinnamon powder. Patch tests with cinnamon oil, 1% in alcohol, gave a 4+ reaction. Cure of the entire eruption followed cessation of contact with cinnamon. The lips and buccal mucous membrane had not been sensitized. Apparently, when the skin is the original surface sensitized, the mucous membranes are seldom sensitized on a clinical level. Contrariwise, when the mucous membrane is the original surface sensitized, the skin almost always shares in the sensitization. Ingestion of cinnamon powder was followed by itching of the hands in 12 hours. Ingestion of cinnamon oil was followed by itching and vesiculation of the hands after five days (delayed reaction) on one occasion and after 12 hours on a second occasion.

A.M.A. Arch. Neurology and Psychiatry, Chicago

65:659-792 (June) 1951

Dandy's Striatal Theory of "Center of Consciousness:" Surgical Evidence and Logical Analysis Indicating Its Improbability. R. Meyers. —p. 659.
Encephalopathy Associated with Acute Diffuse Platelet Thrombosis: Report of Case. A. Hauser, A. Beyer Jr. and R. A. Burger.—p. 672.
Effects of ACTH on Cerebral Blood Flow and Oxygen Consumption. R. W. Alman and J. F. Fazekas.—p. 680.
Familial Occurrence of Tuberous Sclerosis. W. W. Dickerson.—p. 683.
Neurological Complications of Insulin Shock Therapy with Electroencephalographic Studies: Case Studies. L. Halle and J. F. Ross. —p. 703.
Babinski Reflex and Marie-Foix Flexor Withdrawal Reflex: Historical Notes. R. Wartenberg.—p. 713.
Glucose Tolerance in Chronic Schizophrenia and Senile States. W. Simon and J. T. Garvey.—p. 717.
*Postpartum Necrosis of Adenohypophysis with Hypoglycemic Convulsions. E. C. Clark, M. Franklin and A. L. Sahs.—p. 724.
EEG Prognosis in Vascular Hemiplegia Rehabilitation. W. Van Buskirk and V. R. Zarling.—p. 732.
Effect of Electroshock on Blood Pressure in Psychotic Patients. W. W. Igersheimer and J. A. F. Stevenson.—p. 740.
Anticonvulsant Drug Therapy of Behavior Problem Children with Abnormal Electroencephalograms. B. Pasamanick.—p. 752.

Hypoglycemic Convulsions in Postpartum Necrosis of Adenohypophysis.—According to Clark and associates it was not until Sheehan's series of papers appeared that the true nature of hypopituitary cachexia (Simmonds' disease) was understood and that the relation of the clinical syndrome to ischemic necrosis of the adenohypophysis following severe postpartum collapse and hemorrhage was clarified. That hypoglycemia and associated convulsive seizures can occur in this disease was first suggested by Wilder in 1930. Since convulsions may be the presenting symptom, this disorder is of much interest to the neurologist. In the woman whose case is reported the appearance of hypoglycemic convulsions was the dramatic episode that called attention to the diagnosis, although the patient had had premonitory symptoms for 17 years. The immediate therapeutic problem was the control of the Addisonian crisis and associated hypoglycemia. This end was achieved with aqueous and oil-soluble adrenal cortex extract, cortisone, and parenteral injection of sodium chloride and glucose solutions. Recovery has been maintained with daily injections of oil-soluble adrenal cortex extract and thyroid extract by mouth, along with frequent feedings of a high protein and moderate carbohydrate and fat diet. In spite of a grave situation, characterized by a number of convulsions and a period of stupor lasting several weeks, the patient's intellectual functions apparently have not been impaired. It should be recognized that women who have such symptoms as amenorrhea, myxedema, adrenocortical deficiency, hypoglycemia, and

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convulsions may have postpartum necrosis of the adenohypophysis. Emaciation is not necessarily present in this disorder. The recognition of this syndrome and the appropriate therapy may greatly improve the outlook in a condition that heretofore had a poor prognosis in the severe cases.

A.M.A Arch. Otolaryngology, Chicago

53:607-718 (June) 1951

Clinical Evaluation of Substituted Ammonium Saccharins for Nasal Medication. S. L. Fox.—p. 607.
Some Experiences in Management of Cancer of Middle Ear and Mastoid. W. L. Mattick and J. W. Mattick.—p. 610.
Problems of Septum in Rhinoplastic Surgery. O. J. Becker.—p. 622.
Tumors of Larynx: Review of 116 Cases. H. H. Harris and K. L. Wattleworth.—p. 640.
Fifty Years' Progress in Scientific Otolaryngology. A. Lewy.—p. 646.
Brain Abscess of Frontal Lobe Complicating Pansinusitis: Report of Case with Operation and Recovery. B. H. Shuster, C. D. Hinton and A. R. Shuster.—p. 655.
Reconstruction of Orbital Floor Using Stainless Steel Wire Mesh. M. S. Ersner, H. R. Morse and M. H. Alexander.—p. 658.
Primary Aural Cholesteatoma. B. M. Volk.—p. 662.
Exostosis of External Auditory Canal. B. G. McKibben.—p. 668.
Bilateral Contact Ulcer Granuloma Following Endotracheal Anesthesia. W. K. Wright.—p. 670.
Peroral Endoscopy. L. H. Clerf, F. J. Putney and J. J. O'Keefe. —p. 679.

American Journal of Medical Sciences, Philadelphia

221:599-712 (June) 1951

*Acute Rheumatic Fever in Young Adult White Male. J. G. Hirsch and D. M. Flett.—p. 599.
Incidence and Cost of Treatment of Bacterial Endocarditis: Study of All Cases Occurring in Metropolitan Washington in the Year 1948. H. F. Dowling and F. J. Murray.—p. 612.
*Study of Antigen-Antibody Mechanism in Rheumatic Diseases. T. McP. Brown, R. H. Wichelhausen, W. R. Merchant and L. B. Robinson. —p. 618.
Plasma Protein-Bound Iodine Determinations. W. N. Harsha.—p. 626.
Sickle Cell Disease: Studies on "In Vivo" Sickling and the Effect of Certain Pharmacological Agents. A. B. Henderson.—p. 628.
Appraisal of Transorbital Leukotomy. M. T. Moore.—p. 636.
Musical Murmur of Aortic Insufficiency: Clinical Manifestations; Based on a Study of 18 Cases. D. Gelfand and S. Bellet.—p. 644.
Treatment of Urgent Cases of Paroxysmal Auricular Fibrillation. E. H. Hellman, M. R. Altcheck and C. D. Enselberg.—p. 655.
Vasodilator Effects of Priscoline in Patients with Ischemic Extremities. H. Rottenstein, O. Horwitz, H. Montgomery and others.—p. 661.
Digital Cutaneous Blood Flow, Cardiac Output, Blood Pressure and Pulse Rate Immediately Following Administration of Four Potential Vasodilators. A. Sayen, O. Horwitz and M. W. Stroud III.—p. 667.
Measurements of Certain Cardiovascular Responses to ACTH and Cortisone in Man. O. Horwitz, A. Sayen, M. Naide and J. L. Hollander. —p. 669.
Production of Urinary Casts During Use of Cation Exchange Resins. I. S. Friedman, S. Zuckerman and T. D. Cohn.—p. 672.
Observations on Plasma Potassium Level of Man. S. J. Farber, E. D. Pellegrino, N. J. Conan and D. P. Earle.—p. 678.
Effect of Aureomycin on Venous Clotting Time. W. A. Blodgett and F. J. Schilling.—p. 688.
Recent Trends in Breast Feeding: Review. N. R. Newton and M. N. Newton.—p. 691.
Idiopathic Scoliosis. A. M. Bestebreurtje.—p. 699.

Rheumatic Fever in Adult Male.—Because of the relatively few observations on the course of active rheumatic fever in young adult white males, the authors report on 109 such cases encountered during 1948 and 1949 at an Army air base in Wyoming. There was evidence of recent beta hemolytic streptococcic infection in almost every case. Migratory polyarthritis and fever were the outstanding clinical manifestations of rheumatic fever in this group. It was found that carditis could be demonstrated electrocardiographically in a high percentage of cases, provided daily tracings were taken. Sinus bradycardia was found during the acute phase of the rheumatic attack with surprising frequency. Though the total disease characteristically ran a benign course, organic heart murmurs appeared and persisted in 17.4% of the cases. Mitral insufficiency and aortic insufficiency were the two predominant valvular lesions developing. Moderate doses of acetylsalicylic acid (aspirin) were probably effective in alleviating symptoms but were ineffective in shortening the course of the illness or in preventing the development of valvular heart disease.

Antigen-Antibody Mechanism in Rheumatic Diseases.—Brown and co-workers regard the effectiveness of corticotrophin (ACTH) and cortisone in rheumatic diseases as evidence of the allergic nature of these diseases. Since adrenal cortical hormones are known to block antigen-antibody reactions without destroying the antigen, this is presumed to be the mechanism of its action in rheumatic diseases and the explanation for the relapses that occur when it is discontinued. The authors suggest that the antigen in the rheumatic diseases is provided by the pleuropneumonia group of organisms, which are intermediate in their properties between bacteria and viruses. However, because the size of these organisms makes them invisible in tissues and their fastidious growth requirements make it difficult to culture and subculture them, their etiological relationship has not yet been proved. Indirect evidence that they may play a role is provided by the parallel between their in vitro response to antibiotics and the in vivo response of rheumatic diseases to the same antibiotics. Often antibiotics to which the organisms are sensitive produce exacerbations in symptoms, presumably due to the liberation of increased amounts of antigen from the destroyed organisms. In other less sensitive patients antibiotic therapy produces temporary improvement. The authors also found that they were able to reduce the antibody-containing serum globulins in patients with rheumatoid arthritis by administering 2.5 to 10 gm. of human serum albumin intravenously. This effect was comparable to that obtained from cortisone therapy. It was accompanied by a decrease in joint pain and swelling that lasted six to eight hours. A combination of chloramphenicol and albumin produced even more remarkable improvement. Human serum albumin also appeared to influence favorably two cases of serum sickness, one severe penicillin reaction, and one case of acute conjunctivitis in Reiter's disease.

American Journal of Orthopsychiatry, New York

21:223-444 (April) 1951. **Partial Index**

Psychopathic Behavior in Infants and Children: Critical Survey of Existing Concepts. B. Karpman and others.—p. 223.
Some Considerations Relating to Genesis of Autistic Behavior in Children. J. L. Despert.—p. 335.
The Neurotic Child and His Mother: Psychoanalytic Study. M. Sperling. —p. 351.
Adolescent Alternation of Anorexia and Obesity. I. N. Berlin, M. J. Boatman, S. L. Sheimo and S. A. Szurek.—p. 387.

Am. J. Roentgenol. & Rad. Therapy, Springfield, Ill.

65:853-1026 (June) 1951

Role of Roentgenology in Gastroenterology: Caldwell Lecture, 1950. H. L. Bockus.—p. 853.
Acute Appendicitis with Radiopaque Appendiceal Lithiasis. E. G. Laforet, J. J. Greenler and E. J. O'Brien Jr.—p. 867.
Prolapse of Lower Lip of Ileocecal Valve into Terminal Ileum. L. G. Rigler and E. Lasser.—p. 878.
Porphyria: Cause of Nonspecific Small Intestinal Disturbance. S. H. Fisher and R. R. Stanley.—p. 882.
Limited Usefulness of "Positive Pressure" Chest Roentgenogram in Pulmonary Tuberculosis. B. Pollak and A. Hurst.—p. 886.
*Osteonephropathy in Children. J. J. Cancelmo and R. S. Bromer.—p. 889.
Air Cells in Great Wing of Sphenoid Bone. R. Wigh.—p. 916.
Infantile Cortical Hyperostosis: Familial Disease? J. G. Boyes and N. G. Demy.—p. 924.
Case of Letterer-Siwe Disease. C. W. Schwartz.—p. 931.
Dose-Time Relationship for Cure of Squamous Cell Carcinoma. J. R. Andrews and T. O. Coppedge.—p. 934.
Irradiated Human Plasma and Phagocytosis. J. N. Sarian.—p. 940.
Physical Aspects of Rotation Therapy with Betatron: Part I. J. S. Laughlin, R. A. Harvey, L. L. Haas and others.—p. 947.

Osteonephropathy in Children.—The term osteonephropathy includes a variety of closely related but distinct syndromes in which there are bone changes associated with renal disease. These are renal rickets, nephrocalcinosis, the Fanconi syndrome, and idiopathic hypercalcuria. Two of these entities, renal rickets and nephrocalcinosis, are discussed in detail with presentation of eight cases of the former and one of the latter. The bone changes in renal rickets resemble a combination of rickets and hyperparathyroidism, with one or the other predominating. The roentgen appearance of long bones is sufficiently characteristic to enable one to make the diagnosis of renal rickets in a great majority of the cases. Cortical erosions are an important diagnostic clue, but it is difficult to differentiate primary hyperparathyroidism from renal rickets on the basis of the bone changes alone. Fortunately, primary hyperparathyroidism in children is an extremely rare disease. The roentgen appearance of the long bones in nephrocalcinosis differs in no way from ordinary

rickets. Renal calcifications, if present, may be suggestive, but the final clinical diagnosis cannot be made without a complete history, physical examination, and laboratory study. If sufficient renal impairment is present in primary hyperparathyroidism, the bone lesions could be indistinguishable from renal rickets. The diagnosis could then only be made after exhaustive clinical and laboratory studies. In primary hyperparathyroidism, there is almost always elevation of the serum calcium level as opposed to the normal or slightly depressed serum calcium level found in renal rickets.

Annals of Western Medicine & Surgery, Los Angeles

5:437-516 (May) 1951

*Phonocardiographic Follow-up in Cardiac Surgery. F. M. Groedel, L. Breidenbach and M. Miller.—p. 445.
Outline of Treatment of Pulmonary Tuberculosis. L. Hyde and B. Hyde. —p. 453.
Hernia Repair with Cotton: Preliminary Study with 337 Cases. F. R. Parks.—p. 457.
Simultaneous Occurrence of Multiple Primary Malignant Lesions: Case Report. J. Gaster.—p. 461.
Recent Trends in Psychiatry. S. Futterman.—p. 465.
Low-Back Pain and Its Relation to Lumbar Intervertebral Disks. H. M. Cuneo.—p. 469.
Islet Cell Tumor of Pancreas: Case Report. H. B. Alexander and L. H. Solomon.—p. 472.
Results from Removal of Smallpox and Acne Scars. D. E. Barker. —p. 475.
The Effect of Pregnancy on Otosclerosis. E. Pearson.—p. 477.
Television—Psychiatric Aspects. P. Solomon.—p. 483.
Herpes Zoster Appearing During Cortisone Therapy: Case Report. H. C. Fishman.—p. 487.

Phonocardiography and Cardiac Surgery.—The graphic recording of the heart sounds (phonocardiography) is a much more objective and reliable method of studying functional changes in the heart than is auscultation. Moreover, simultaneous phonocardiograms and part-electrocardiograms yield a more accurate estimate of ventricular systole than any other method. For these reasons phonocardiography was used to study the functional changes in the cardiovascular system in three patients following operations for coarctation of the aorta, rheumatic mitral stenosis, and tetralogy of Fallot, respectively. The systolic murmur in the first case and the diastolic murmur in the second disappeared, while the systolic apical murmur in the third case was highly attenuated. In the patient with coarctation of the aorta, the hemodynamic systole, which was normal before operation, was temporarily shortened after operation but soon returned to normal. In the patient with mitral stenosis the preoperatively shortened systole was distinctly prolonged postoperatively, although not the normal value. In the patient with tetralogy of Fallot systole was constantly normal. The authors recommend this combination of phonocardiography and electrocardiography in the evaluation of the effects of cardiac operations.

Bulletin of Johns Hopkins Hospital, Baltimore

88:499-580 (June) 1951

Electrophysiological Studies of Nerve and Reflex Activity in Normal Man: IV. Two-Neurone Reflex and Identification of Certain Action Potentials from Spinal Roots and Cord. J. W. Magladery, W. E. Porter, A. M. Park and R. D. Teasdall.—p. 499.
Id.: V. Excitation and Inhibition of Two-Neurone Reflexes by Afferent Impulses in Same Nerve Trunk. J. W. Magladery, R. D. Teasdall, A. M. Park and W. E. Porter.—p. 520.
Id.: VI. Excitation and Inhibition of Two-Neurone Reflexes by Impulses in Other Nerves. R. D. Teasdall, A. M. Park, W. E. Porter and J. W. Magladery.—p. 538.
Id.: VII. Certain Effects of Brief Stretch. A. M. Park, R. D. Teasdall and J. W. Magladery.—p. 549.

Cincinnati Journal of Medicine

32:167-212 (May) 1951

Look Ahead in Public Health. L. A. Scheele.—p. 167.
Full-Payment Insurance Plan. D. W. Heusinkveld and C. S. Mundy. —p. 173.

32:213-252 (June) 1951

Endometriosis of Small Bowel Causing Acute Intestinal Obstruction: Report of Two Cases. H. L. Floyd and D. E. Earley.—p. 214.

Journal Clin. Endocrinology, Springfield, Ill.

11:559-662 (June) 1951

Use of Delta⁵-Pregnenolone in Various Clinical Disorders. T. H. McGavack, J. Chevalley and J. Weissberg.—p. 559.
Studies of Urinary 17-Ketosteroid Excretion by Means of New Micro-Chromatographic Fractionation Procedure. A. S. Zygmuntowicz, M. Wood, E. Christo and N. B. Talbot.—p. 578.
Late Results in Treatment of Thyrotoxicosis with Goitrogenic Compounds. E. Rose and J. M. Shorey.—p. 597.
Serum Inorganic Phosphorus in Diagnosis of Diabetes Mellitus. N. G. Schneeberg.—p. 602.
*Sex-Linked Juvenile Diabetes Mellitus: Genetic and Clinical Study of Family. O. B. Barker, R. R. Commons and E. K. Shelton.—p. 608.
Spermatogenesis and Apparent Fertility in Eunuchoid Male in Eleventh Year of Androgen Therapy. S. C. Werner.—p. 612.
Inhibition of Cervical Thyroid Gland by Functioning Struma Ovarii. M. Perlmutter and M. Mufson.—p. 621.
Chromaffin Cell Tumor Simulating Malignant Hypertension: Report of Case with Surgical Cure. W. A. Pratt.—p. 630.

Sex-Linked Juvenile Diabetes Mellitus.—This report presents a genetic and clinical study of a family of eight persons (three boys, three girls, and their parents). The father and the three girls are of average height and have brown hair and eyes; the mother and the three boys have blond hair and blue eyes. The growth curves of the boys and their mother fall within the lowest 1% of the normal range. The boys have diabetes mellitus. The other members of the family show no dextrose intolerance. The family history was traced back for three generations, and it is believed that the diabetes mellitus is probably inherited as a sex-linked recessive characteristic with heterozygous parents. Considered mathematically, growth retardation and blondness in the same siblings are thought to be inherited as recessive autosomal characteristics from a homozygous mother and a heterozygous father.

Journal of Immunology, Baltimore

66:297-404 (March) 1951

Specificity of Radioiodinated (I^{131}) Immune Globulin as Determined by Quantitative Precipitin Reaction. S. P. Masouredis, L. R. Melcher and D. C. Koblick.—p. 297.
Influence of Polymorphonuclear Leukocytes and Macrophages on Antibody Production. T. E. Walsh and C. A. Smith.—p. 303.
Antitoxin Response to Repeated (Daily) Doses of Diphtheria Toxoid. E. Carlinfanti.—p. 311.
Antibody Response to Mumps Vaccine as Evaluated by Complement Fixation and Serum-Virus Neutralization Tests. A. Hoyt, T. M. Eby, P. Ashton and M. V. Veldee.—p. 317.
Production of Potent Anti-Human Globulin (Coombs Reagent) in Rabbits Immunized with Serum Adjuvant Mixtures. C. P. Emerson, W. Franklin and F. C. Lowell.—p. 323.
Some Observations on Host-Cell-Virus Relationships in Fowl Pox: I. Growth in Tissue Culture: II. Inclusion Produced by Virus on Chick Chorio-Allantoic Membrane. F. B. Bang, E. Levy and G. O. Gey. —p. 329.
Mouse Encephalomyelitis: Immunologic Studies of Non-Infected Colony. D. J. Dean.—p. 347.
Evidence of Resistance to Tumor Graft in Early Stages of Induced Oncolysis. P. M. Aptekman and M. R. Lewis.—p. 361.
Factors Involved in Haemagglutination by GDVII Strain of Murine Encephalomyelitis Virus. L. B. Fastier.—p. 365.
Influence of ACTH and Cortisone on Histamine and Anaphylactic Shock in Guinea Pig. S. Malkiel.—p. 379.
Adsorptive Behavior of Bacteriophage T2 with Certain Inorganic Materials. C. C. Shepard and W. G. Woodend.—p. 385.
Agglutinating Antibodies in Serum and Feces. W. L. Barksdale and A. Ghoda.—p. 395.

66:405-486 (April) 1951

Effect of FA and Lansing Viruses on Cholinesterase Activity of Brain and Spinal Cord Homogenates. J. M. Little and R. B. Lawson.—p. 405.
Method for Estimating Capacity of Influenza Virus to Effect Antigenic Modification of Red Blood Cells. F. S. Stewart and J. J. Quilligan Jr. —p. 411.
Tuberculin Type Sensitivity to Spinal Cord Antigen in Rabbits with Isoallergic Encephalomyelitis. B. H. Waksman and L. R. Morrison.—p. 421.
Experimental Determination of Hypersensitive Diathesis in Man. W. P. Creger, Sun Hak Choy and L. A. Rantz.—p. 445.
Experimental Hypersensitivity in Rabbit: Disappearance Rates of Native and Labelled Heterologous Proteins from Serum After Intravenous Injection. D. Gitlin, H. Latta, W. H. Batchelor and C. A. Janeway. —p. 451.
Further Observation of Effect of Acridines on Growth of Viruses. M. D. Eaton, F. S. Cheever and C. G. Levenson.—p. 463.
Mixed Infection of Bacterium with Coli-Dysentery Phage T5 and Serologically Related Salmonella Phage. M. H. Adams.—p. 477.

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Journal Nat. Cancer Inst., Washington, D. C.

11:663-866 (Feb.) 1951. **Partial Index**

Leukemoid Reactions to Transplanted Mouse Tumors. J. C. Bateman. —p. 671.
Study of "Gruskin Serological Test" for Detection of Cancer: Precipitation of Blood Proteins by Alcohol. N. Holmgren, R. W. Denton, S. A. Levinson and others.—p. 689.
Studies of Various Tests for Malignant Neoplastic Diseases: I. Reduction of Methylene Blue by Plasma. N. Eriksen, L. D. Ellerbrook and S. W. Lippincott.—p. 705.
Measurement of Proliferation in Tissue Cultures by Enumeration of Cell Nuclei. K. K. Sanford, W. R. Earle, V. J. Evans and others. —p. 773.
Excretion of Radioactivity During Four-Day Period Following Feeding of Carbon 14-Labeled 2-Acetylaminofluorene to Rats. J. H. Weisburger, E. K. Weisburger and H. P. Morris.—p. 797.
Effect of Ingestion of Thiouracil on Strain C Mice. H. P. Morris, C. D. Green and A. J. Dalton.—p. 805.
Production of Malignancy in Vitro: XII. Behavior of Recovery Cultures. E. Shelton and W. R. Earle.—p. 817.
Effect of Podophyllotoxin on Skin of Mouse, with Reference to Carcinogenic, Cocarcinogenic, and Anticarcinogenic Action. I. Berenblum. —p. 839.
Action of Croton Oil in Induction of Sarcomas in Mice. M. Klein. —p. 843.
Observations on Properties of Leukemic Cells Resistant to Folic Acid Antagonists. L. W. Law.—p. 849.

Journal of Thoracic Surgery, St. Louis

21:543-650 (June) 1951

Consideration of Some of the Problems in Cardiovascular Surgery. A. Blalock.—p. 543.
Experimental Reconstruction of Tracheal and Bronchial Defects with Stainless Steel Wire Mesh. R. M. Bucher, W. E. Burnett and G. P. Rosemond.—p. 572.
Shoulder Girdle Dysfunction Following Thoracoplasty Combined with Partial Scapulectomy: Study of 23 Patients During Two-Year Period. H. B. Doppelt and J. Goldberg.—p. 584.
Pulmonary Decortication for Clotted Hemothorax Following Idiopathic Spontaneous Hemopneumothorax. G. P. Seley and H. Neuhof.—p. 600.
Posterior Mediastinal Tracheotomy. H. Sloan and R. A. Cowley.—p. 602.
*Bullet Embolus to Left Femoral Artery Following Thoracic Gunshot Wound: Probable Entrance Through Thoracic Aorta: Case Report and Résumé of Peripheral Arterial Bullet Emboli. J. L. Keeley.—p. 608.
Effect of Decreasing Amount of Lung Tissue on Right Ventricular Pressures in Animals. R. F. Carlson, B. C. Charbon, H. G. A. Charbon and W. E. Adams.—p. 621.

Bullet Embolus to Femoral Artery Following Thoracic Gunshot Wound.—The man whose case is presented was shot in the right arm and right flank. Half an hour later he noticed pain in his left groin and soon thereafter pain throughout his entire left leg with inability to walk. One bullet entered just anterior to the right greater trochanter, the other went through the soft tissues posterior to the right humerus and entered the chest through the fifth interspace. The left leg was cold and paralyzed below the knee. Roentgenograms showed no foreign body in the chest where one was expected, but the shadows of two bullets were present in the film of the pelvic region. The bullet that had entered the right hip lay along the inferior ramus of the right pubic bone. The other bullet lay in the position occupied by the left femoral artery immediately over the head of the left femur at the point where the profunda artery arises. It was thought at first that the bullet that entered the region of the right hip had damaged the lumbosacral plexus, causing paralysis. A neurosurgical consultant felt that a vascular occlusion was the cause. The bullet was found in the artery just at the point where the profunda branch arises. It was extracted. This appears to be the sixth case of its kind with survival of the patient. In addition, 15 other cases in which bullet wounds of the heart or associated great vessels had been followed by peripheral arterial embolization of the foreign body are summarized. Study of these cases suggests that a thoracic wound with a small caliber missile may do no serious damage to the lungs and pulmonary vessels but still may have sufficient force to pierce one wall of the aorta or of a cardiac chamber. It may then be embolized immediately or later to the systemic vessels, being carried usually to the iliac or femoral vessels and more commonly to the left side. In bullet wounds with only a wound of entrance, failure to demonstrate the foreign body in the expected region should cause suspicion that it may have entered the cardiovascular system and been carried away. Other parts of the body should be studied roentgenographically. The correct diagnosis should be followed by early embolectomy.

New England Journal of Medicine, Boston

244:859-892 (June 7) 1951

*Carcinoma of Colon and Rectum: Observations on Massachusetts General Hospital Cases, 1937-1948. C. E. Welch and W. P. Gidings. —p. 859.
*Clinical and Epidemiologic Observations of Coxsackie-Virus Infection. G. Dalldorf and R. Gifford.—p. 868.
Acute Mediastinal Emphysema Complicating Eclampsia. R. W. Kistner. —p. 873.
Unexpected Ultra-Violet Ray Burn Received in Unusual Manner. J. G. Downing, J. W. Baird and J. W. Wyman.—p. 876.
Management of Acute Frontal Sinusitis. R. L. Goodale.—p. 877.

Carcinoma of Colon and Rectum.—Reported results of treatment in cancer of the colon and rectum are characterized by extreme disparity. The surgeon who discards cases not operated on, those in which only palliative resection was done, deaths from operations, later deaths from extraneous causes, and patients who have not been followed, obviously will have a comparatively high percentage of "cancer cures," but such a system is manifestly unfair to anyone who wishes to consider the entire problem of cancer of the colon and rectum. The two best methods of calculating survival rates are (1) inclusion of all cases appearing in a given clinic or geographical area and (2) calculation of survival rates on the number of patients on whom resections for cure are performed. This paper analyzes 1,876 cases of carcinoma of colon and rectum that were observed at the Massachusetts General Hospital from 1937 to 1948. Of this number, 1,088 were seen between 1937 and 1943, and the five-year survival rate was determined for this group. Over-all figures indicate that 77% of the patients who entered the hospital with cancer of the colon and rectum from 1937 to 1948 had resection of the involved bowel. The resectability increased from 72% in 1937-1943 to 81% in 1944-1948. Five-year survivals were obtained in only 25% of those observed from 1937 to 1943. If the results are calculated on the basis of operative survivals with resections for cure, 45% survived the five-year period. The latter figure varies, depending on whether lymph nodes are involved (55% when they are not involved; 26% when metastases are present). Prophylactic colectomy should be performed in ulcerative colitis and multiple polyposis. Polyps of the rectum or low sigmoid may be treated by fulguration through the sigmoidoscope when the pedicle is long and benign. If after a polyp has been removed through the sigmoidoscope the pathologist returns a diagnosis of cancer, a radical operation should usually be performed. Resection of a segment of the colon and mesentery should be done when the polyp is in the sigmoid or higher. Complete left colectomy is required if metastatic nodes are found during a resection for cancer of the sigmoid or left colon. Resection of tumors of the lower sigmoid and intraperitoneal rectum with anastomosis should not be done unless at least 5 cm. of normal bowel and pericolic tissue can be obtained below the tumor. Unfortunately, nearly two-thirds of all patients with cancer of the colon and rectum are incurable when they reach the hospital. Further improvement in therapeutic results will depend on routine proctosigmoidoscopy as an integral portion of the physical examination.

Coxsackie Virus Infection.—Coxsackie virus was first identified during a study of five small outbreaks of poliomyelitis in New York during the summer of 1947. The first strains were isolated from two paralyzed boys in the village of Coxsackie. The other epidemics in New York that year did not yield Coxsackie virus, but a number of isolations, including a second serologic type, were made later from specimens collected during the summer of 1947 in Wilmington, Del. During 1948 and 1949 the search was widened in New York, and 24 isolations were made, including additional types and a second variety, Coxsackie virus group B. This report summarizes the clinical and epidemiological observations made during these three years. The data are derived largely from the records of 517 patients whose feces were tested for pathogenicity for suckling mice. Of the 517 cases tested, 30 (5.8%) yielded Coxsackie virus. The virus was commonest in younger children and during the late summer months. The clinical records of "poliomyelitis" patients from whom Coxsackie viruses were isolated did not differ significantly from the records of patients from whom virus was not isolated. The percentage of specimens that contained virus was greatest in 1947 and least in 1949. There was an inverse relation between

the frequency of isolation of Coxsackie virus and the frequency of paralysis by year. If such a difference occurred consistently it would afford one means of distinguishing between poliomyelitis epidemics that are and those that are not complicated by the presence of Coxsackie-virus infection.

Ohio State Medical Journal, Columbus

47:393-488 (May) 1951

Treatment of Diabetes. J. I. Goodman.—p. 417.
*Effect of Histamine on Marchiafava-Micheli Syndrome (Paroxysmal Nocturnal Hemoglobinuria). E. J. Stefanic, H. F. Loyke and M. A. Kraft.—p. 424.
Weber-Christian Disease: Report of Two Cases, One with Autopsy. F. R. Hanrahan Jr., V. D. Ippolito and R. W. Dilworth.—p. 427.
Unusual Intra-Abdominal Hernias: With Case Reports. R. E. Pickett. —p. 430.
*Heterotopic Pregnancy—(Combined Intra-Uterine and Extra-Uterine Pregnancy). C. J. Derby and R. C. Miller.—p. 433.
Schizophrenia Treated with Insulin Shock Followed by Electroshock Therapy. D. M. Palmer and E. S. Garrett Jr.—p. 435.
Modern Concept of Glaucoma. H. H. Insel.—p. 438.

Histamine in Marchiafava-Micheli Syndrome.—The history is presented of a man, 42, with slight jaundice, weakness, an enlarged spleen and liver, and paroxysmal hemoglobinuria. This and the positive Ham-Horack test classified the case as one of Marchiafava-Micheli syndrome, also known as paroxysmal nocturnal hemoglobinuria. The literature on the therapy of this condition indicates that neither blood transfusion nor splenectomy, nor various other treatments produce satisfactory results. It appears that the red blood cells in these patients have for some reason become sensitized to a potential lysin present in the patient's own serum and in normal serum. Working on this hypothesis, one of the authors of this paper attempted to desensitize the patient with histamine diphosphate. This was first given intravenously in a dose of 2.75 mg. in 250 cc. of isotonic solution of sodium chloride. After eight consecutive days of therapy the Ham-Horack test showed no hemolysis between the patient's cells and serum and only partial hemolysis between the patient's cells and normal serum. After another 12-day course of histamine the Ham-Horack test again showed the same results. Eighteen days later, the test had become completely negative for hemolysis of the patient's red blood cells between both the patient's serum and normal serum. When it was found that the anemia persisted (erythrocyte count between 2 and 2.9 million and hemoglobin of 45 to 49%), the bone marrow was examined and erythroblastic hyperactivity was discovered. Skin tests, which were made because of a history of urticaria, remained negative. Liver biopsy disclosed normal tissues but hemosiderosis. It was decided to resume histamine desensitization, but this time via the subcutaneous and later the intramuscular route. Later, because there was no improvement in the anemia and because there was again hemolysis between the patient's cells and normal serum, the intravenous administration of histamine was resumed. After this the Ham-Horack test showed negative hemolysis between the patient's cells and both normal and his own serum. The intravenous administration of histamine has been continued to date, but the anemic picture remains unchanged. It is suggested that there may be an altered phospholipid cholesterol ratio in the stroma of the red blood cells.

Heterotopic Pregnancy.—The woman whose case is presented had had her last menstrual period on Oct. 10, 1949. She had two living children but no miscarriages. She complained of lower abdominal pain and vaginal bleeding. Pelvic examination revealed a soft uterus enlarged to the size of a two and one-half to three month pregnancy and marked tenderness in the left adnexal region. Sedatives and bed rest were ordered, and the vaginal bleeding subsided. One week later, on Jan. 3, 1951 she had severe cramps in the left lower quadrant and vaginal spotting and was in mild shock. She was hospitalized with a provisional diagnosis of ruptured left tubal pregnancy. Exploratory laparotomy revealed a large quantity of blood in the peritoneal cavity. The left tube was distended with a ruptured tubal pregnancy. The fundus was soft and symmetrically enlarged to about the size of a two and one-half to three month pregnancy. The pregnant tube, left ovary, and the appendix were removed, and the abdomen was closed. After the operation the woman was seen at monthly intervals. A full-term living female infant was delivered in July. Ectopic pregnancy is said to occur about once in every 300 normal pregnancies, and the incidence of combined pregnancy is about one in 30,000 pregnancies. The preoperative diagnosis of heterotopic pregnancy is a difficult one, because of concomitant enlargement of the uterus. Cul de sac tenderness with a soft enlarged uterus should bring to mind the possibility of such a diagnosis. A second sign of double pregnancy is the presence of two corpora lutea in the ovaries, indicating the possibility of two conceptions.

Southern Medical Journal, Birmingham, Ala.

44:467-570 (June) 1951. **Partial Index**

Multiple Myeloma: Its Treatment with Urethane and ACTH. R. D. Haines, W. N. Powell and H. A. Bailey.—p. 467.
Gastric Double Contrast. C. Giantturco.—p. 478.
Tumors of Jaws. J. C. Glenn Jr., A. Taylor and R. J. Reeves.—p. 481.
Melanoma of Urinary Tract and Prostate Gland. O. S. Lowsley.—p. 487.
*Most Detectable Internal Cancer. R. H. Overholt.—p. 493.
Fat Embolism: Report of Six Cases. R. B. Ray.—p. 499.
*Frequency of Cancer of Lung in All Malignancies Studied at Autopsy. R. H. Rigdon and H. Kirchoff.—p. 506.
Newer Concepts in Treatment of Pulmonary Tuberculosis. H. L. Mantz. —p. 512.
Report of Three Years Activities in Veterans Administration Tuberculosis Rehabilitation Center. B. B. Bagby Jr.—p. 516.
Tuberculosis in Pregnancy, Labor and Puerperium J. M. Reese and C. W. Martin.—p. 523.
Natural Childbirth Illusion. A. J. Mandy, R. Farkas, E. Scher and T. E. Mandy.—p. 527.
Treatment of Endometriosis. D. D. Wallace.—p. 534.
Treatment of Idiopathic Pruritus Ani with Adenosine-5-Monophosphate. J. G. Matt.—p. 537.
Problems and Opportunities of Psychosomatic Practice in General Hospital. R. W. Garnett Jr.—p. 542.
Simplified Method of Cryotherapy for Acne Vulgaris. W. L. Dobes. —p. 546.
Problem of Diabetic Retinopathy. R. Day.—p. 549.
Timing in Convalescence from Myocardial Infarction. N. S. Stern. —p. 551.
Health Maintenance in Small Plants. L. M. Petrie.—p. 555.

Detection of Lung Cancer.—Early detection and cure rates should be higher for lung cancer than for cancer of any other internal organ for two reasons: 1. The lungs can be screened more readily on a mass production basis than any other organ, because the subject does not have to be seen by the physician. 2. Small cancers a few millimeters in diameter produce detectable shadows in survey roentgenograms. In various surveys the incidence of primary neoplasms of the lung among patients with asymptomatic lesions discovered by roentgenography has varied from 35 to 74%. Exploratory thoracotomy is necessary to establish the diagnosis in many cases; negative bronchoscopic or cytological examinations should not be used as evidence of the absence of cancer. In Overholt's experience with 863 cases of primary cancer of the lung, 75% of the asymptomatic patients had localized lesions with no evidence of spread, whereas this was true of only 11% of the symptomatic cases. The lesions were resectable in 100% of the asymptomatic group and in 30% of the symptomatic group. The five year cure rate for the symptomatic group was 11%. If current trends continue, the cure rate for the asymptomatic patients will be 75%.

Incidence of Lung Cancer.—These authors believe that the alleged increase in the incidence of cancer of the lung is more apparent than real. In a review of 6,663 autopsies performed between 1920 and 1949 they found 1,017 cases of cancer, of which 67 were cancers of the lung. From their material and from the literature they concluded that the frequency of cancer of the lung relative to all malignant tumors is similar to that observed 25 to 50 years ago. They believe that lung cancer, which is commonest in the sixth decade of life, appears to be increasing only because a larger proportion of the population now reach this age. They also believe that data on the incidence of lung cancer obtained from death certificates are not reliable, since many supposed tumors of the lung are metastatic rather than primary. Finally, they observe that since 92.5% of lung cancers occur in males and 83.5% in the white race, as contrasted with the Negro race, both sex and race may play some role in the pathogenesis of this tumor.

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FOREIGN

Acta Obstet. et Gynec. Scandinavica, Stockholm

30:359-454 (No. 4) 1951

Diagnosis and Treatment of Genital Tuberculosis in Women. S. O. Liljedahl and Å. B. V. Rydén.—p. 359.
*Spinal Anaesthesia as Treatment of Postpartum Atony of Uterus. F. Fuchs.—p. 384.
Review of Pelvic Tumors Arising Extragenitally and Obstructing Delivery. K. Haeger.—p. 391.
Spontaneous Rupture of Uterus During Pregnancy. T. Hølund.—p. 408.
Maintenance of Early Pregnancy Despite Extirpation of Three Corpora Lutea. K. Kulseng-Hanssen.—p. 420.
Potassium Deficiency in Hyperemesis Gravidarum. N. Bergqvist.—p. 428.
Case of Supernumerary Ureter Opening Extravesically. C. J. Carlsen. —p. 439.

Spinal Anesthesia for Post Partum Atony of Uterus.—In 1942 Hansen reported four cases of post partum atony of the uterus in which spinal anesthesia proved effective. Since that time this treatment has been used in eight other women (in one of them in two births). Each time the desired effect was obtained. The hemorrhage varied from 800 to 1,900 ml. One patient was in deep shock before the spinal anesthesia was given, yet the effect was prompt and life-saving. It is important that the blood lost be replaced by blood transfusion. The method should be used before the blood loss exceeds 750 ml., if the blood pressure shows signs of falling, when it is certain that the placenta is intact, and when pituitary extract and ergot preparation and compression of the aorta have had no effect. Should the method fail, hysterectomy can be performed as a last resort without further anesthesia. A 3.5% solution of procaine hydrochloride was used in all cases; from 10 to 12 ml. were injected in the course of four or five minutes. The blood pressure fell in most cases, but this could be counteracted by means of ephedrine. The blood transfusions contributed to the recovery.

Australian and New Zealand J. Surgery, Sydney

20:245-318 (May) 1951

Technique of Gastrectomy. L. Doyle.—p. 245.
Squamous Epithelium in Encysted Hydrocele of Cord: Note on Squamous Epithelium of Peritoneal Origin. E. S. J. King.—p. 265.
Observations on Surgical Anatomy of Thoraco-Lumbar Sympathetic System. K. C. Bradley.—p. 272.
*Sequelae of Treatment of Hydatid Cysts of Lung. S. C. Fitzpatrick. —p. 278.
Technical Aspects of Surgery of Hypertension with Follow-Up of Fifty Cases. D. Miller.—p. 285.
Diaphragmatic Deformation of Liver. G. S. Christie.—p. 289.

Hydatid Cysts of Lung.—When an unruptured hydatid cyst of the lung is completely removed surgically, the patient usually has a smooth convalescence and serious sequelae are uncommon. When patients are first seen with the cyst already ruptured, complications will be more frequent and the mortality rate will approximate 5%. The main sequelae are: (1) anaphylactic shock; (2) lung hydatid abscess, persistent cavity, and chronic empyema; (3) recurrence of daughter cysts; and (4) fibrosis and bronchiectasis. This report is based on observations on 80 cases of hydatid cysts of the lung, of which 70 have been followed up. Fifty of these patients, who have been under observation for one to 28 years, show no sign of persisting pulmonary lesion attributable to hydatid cysts of the lung. The postoperative course was unsatisfactory in the remaining 20 cases. There were four deaths following operation. After briefly reporting the histories of these four patients, the author discusses the prevention and treatment of the four groups of sequelae.

British Journal of Dermatology, London

63:203-240 (June) 1951

*Kaposi's Varicelliform Eruption: Record of Outbreak. J. Sommerville, W. Napier and A. Dick.—p. 203.
Acne Vulgaris: Psychosomatic Study. E. Wittkower.—p. 214.
Note on Treatment of Lupus Erythematosus with Vitamin E. J. Morgan. —p. 224.
Acanthosis Nigricans. T. Cochrane and J. O'D. Alexander.—p. 225.
Solar Urticaria (Wave-Length Less Than 3700 Å.). I. Anderson.—p. 230.

Kaposi's Varicelliform Eruption.—This paper describes a group of cases of Kaposi's varicelliform eruption that appeared at the time of widespread vaccination occasioned by the presence of smallpox in Glasgow. Of the 10 patients observed, four were unrelated, two were members of the same household, and four were infected while in hospital for treatment of a preexisting skin condition. All had suffered previous skin damage, and all had had contact with recently vaccinated persons, but were unvaccinated themselves, except for one, who had been vaccinated about a week before his illness. All showed the clinical picture of a grouped pustular eruption situated on an erysipeloid base. Vaccinia virus was recovered in four cases. Two of the 10 patients were only mildly ill and required only local treatment. Four others were moderately febrile for two or three days, appearing to respond favorably to penicillin and a combination of sulfonamides. The remaining four patients had general toxemia, which ended fatally in one case and endangered life in the other three. Penicillin, with or without sulfonamides, had no effect, whereas the administration of aureomycin in two of them appeared to coincide with a significant fall of temperature and striking improvement. Kaposi's title notwithstanding, there is little likelihood of confusion with chickenpox. The resemblance to smallpox, on the other hand, particularly in an adult whose face is affected, may be very striking. Since Kaposi's eruption is highly infectious in susceptible persons, unvaccinated sufferers from eczema should be warned of the danger of exposing themselves to contact with vaccinia. A newly vaccinated person should not be admitted to a hospital ward, particularly a dermatologic ward, without proper precautions to safeguard the other patients. During times of widespread vaccination it would probably be wise to discharge from dermatologic wards patients, particularly children, with allergic eczematous conditions.

British Journal of Radiology, London

24:295-354 (June) 1951

SYMPOSIUM ON RESULTS IN TREATMENT OF CANCER

I. Calculation of Survival and Cure Rates. H. F. Dorn.—p. 295.
II. Presentation of Clinical Results. J. W. Boag.—p. 299.
III. Practical Views on Presentation of Results of Treatment. J. Clemmesen.—p. 305.
IV. Method of Presentation of Results. R. McWhirter.—p. 308.
V. Report of World Health Organization. Committee on Health Statistics.—p. 311.
Relative Value of Radiology in Prevention of Tuberculosis. J. F. Brailsford.—p. 315.
Small Intestine Pattern in Normal Children and in Coeliac Disease: Its Relationship to Nature of Opaque Medium. R. Astley and J. M. French.—p. 321.
Dosage from Radioisotopes Uniformly Distributed Within a Sphere. T. H. Oddie.—p. 333.
Measurement of Skin Dose in Radium Therapy. H. D. Griffith and G. E. Swindell.—p. 337.
Ionization Chambers for Electron Dosimetry. J. W. Boag, F. D. Pilling and T. Wilson.—p. 341.
Lateral Distribution of Ions Across Track of Ionizing Particle: Part II. Further Consideration of Equilibrium Distribution. J. Read.—p. 345.
Effect of Ionizing Radiations on Broad Bean Root. L. H. Gray and M. E. Scholes.—p. 348.

British Medical Journal, London

1:1343-1404 (June 16) 1951

Aspects of Circulation's Economy. K. J. Franklin.—p. 1343.
Low-Salt Diet in Treatment of Congestive Heart Failure. A. L. Nielsen, P. Bechgaard and H. O. Bang.—p. 1349.
Radiation, Light, and Illumination. J. N. Aldington.—p. 1353.
Haemolytic Disease of Newborn Due to Immune Anti-A Agglutinin. A. Zoutendyk and A. Broido.—p. 1357.
*Changes in Sweating After Prickly Heat. W. S. S. Ladell.—p. 1358.
Actinomycosis in the North-East of Scotland. I. A. Porter.—p. 1360.
Potassium Bromate Poisoning. W. A. Parker and J. R. Barr.—p. 1363.
Pregnancy Prolonged Beyond Expected Date. D. Latto.—p. 1364.

Changes in Sweating After Prickly Heat.—A man newly arrived in the tropics was given (in October) an acclimatization test, consisting of five 20-minute cycles of work and rest in a climate of 100 F. (37.8 C.) dry bulb, 93.5 F. (34.2 C.) wet bulb, air movement 50 ft. (17 m.) a minute. Pulse rates, rectal temperatures, and body weights were recorded every 10 minutes; serial samples of sweat were obtained by an arm bag and analyzed for chloride; and water drunk and urine passed were measured. Within a few weeks, and a short while after a severe sunburn, prickly heat developed. The irritation kept him awake at night and he began to complain of lassitude and debility. The condition was exacerbated by exposure to climates in which, although he sweated freely, evaporation was rapid enough to leave the skin sticky

rather than wet; profuse sweating, with perspiration running off the skin, tended to give relief. In March, after he had been going into the climatic chamber three or more times a week for 20 weeks, he was again tested to determine to what extent he had become acclimatized. Changes the reverse of acclimatization were found. He had a mild form of type 2 heat exhaustion, which, in accordance with Selye's terminology, might be called a "disease of adaptation." The adrenal cortex seems to be involved in the control of sweating. Prickly heat would be the stress which, added to the several already imposed by a tropical climate, would rapidly lead to what Selye calls the "exhaustion stage," so that even after apparent recovery the heat tolerance remains diminished.

Canadian Medical Association Journal, Montreal

64:477-570 (June) 1951

Canadian Red Cross School Meal Study. F. F. Tisdall, E. C. Robertson, T. G. H. Drake and others.—p. 477.
*Influence of STH, ACTH and Cortisone upon Resistance to Infection. H. Selye.—p. 489.
Some Psychosomatic Aspects of Dermatology. D. Cappon.—p. 495.
Factors Minimizing Reaction to Operative Procedures. G. S. Fahrni. —p. 500.
Feeding of Athletes. E. H. Bensley.—p. 503.
Blood Alcohol Levels and Intoxication. D. K. Merkeley.—p. 506.
*Treatment of Alcohol Withdrawal Symptoms. R. G. Bell.—p. 510.
Poison Ivy. G. E. Craig.—p. 513.
Medical Rehabilitation of Handicapped in Canada. W. P. Warner.—p. 515.
Accidental Ligation of Hepatic Artery and Its Treatment. P. W. Edgecombe and C. Gardner.—p. 518.
Future of Pathologist in Practice of Medicine: His Status and Prestige. J. H. Fisher.—p. 522.
Special Indications for Rectal Pentothal in Children. D. W. Whyte. —p. 525.

Lowered Resistance to Infection Resulting from Cortisone and Corticotrophin.—It became evident in animal experiments that toxic doses of cortisone and corticotrophin (ACTH) usually cause death as a result of unbridled bacterial proliferation. This usually starts in the lung and leads to pulmonary abscess formation, but eventually it may evoke the picture of general septicemia with abscesses in the liver, spleen, kidneys, and sometimes other organs. The increasing clinical use of these hormones revealed that they also predispose patients to infection. In particular, they may reactivate dormant foci of pulmonary tuberculosis. Similarly, in certain types of pneumonia, corticotrophin and cortisone may promote the invasion of the causative microorganisms into the general circulation. The mechanism through which corticotrophin and cortisone diminish resistance to infection is not yet clearly understood, but theoretic considerations led Selye to suspect that the inhibitory effect of these hormones on granuloma formation (and the consequent encapsulation of infectious foci), their destructive effect on lymphatic tissues, as well as their general catabolic effects, might be involved. Since in all these respects the somatotrophic hormone (STH) acts as an antagonist of corticotrophin, he felt that it would be of interest to establish, by animal experiments, whether somatotrophic hormone could raise resistance to infections. Experiments performed on rats to ascertain this revealed that both cortisone and corticotrophin, when given in toxic doses, can cause fatal systemic infections that are presumably due to otherwise nonpathogenic micro-organisms, such as are normally present in the body. This effect of cortisone and corticotrophin can be completely prevented by suitable doses of purified somatotrophic hormone.

Treatment of Alcohol Withdrawal Symptoms.—One of the most successful treatments for the intoxicated alcohol addict consists in the intravenous injection of dextrose, insulin, and a solution of vitamin B complex. However, the contraindications of severe heart disease, hematemesis, and inaccessible superficial veins must be kept in mind. The injection is prepared by adding to a 50 cc. vial of 50% dextrose an amount of standard insulin estimated on the basis of age and weight (from 10 to 50 units) and a solution of vitamin B complex containing a minimum of 20 mg. of thiamine and 200 mg. of nicotinamide. This mixture is drawn into a 50 cc. syringe and injected slowly into one of the cubital veins. An optimum reaction is one in which the patient begins to perspire and goes to sleep approximately one hour after the injection. This reaction is allowed to proceed for a minimum of 30 to 45 minutes before it is terminated with 50 cc. of 50% dextrose given intravenously, preferably into a different vein than the one used for the original injection. Usually, the reaction is terminated with a sweet drink. If no reaction occurs after 90 minutes, it is permissible to inject an additional 10 or 20 units of insulin intramuscularly. From the time of injection, until the insulin reaction is completed, it is imperative that a nurse be in constant attendance on the patient and that a physician be immediately available. When a good initial reaction has been obtained, a patient may benefit from a second reaction of this type at any time after a six hour interval. In the chronic phase of alcohol addiction the injection has been repeated three times within the first 36 to 48 hours in order to more rapidly restore normal sleeping and eating habits. A satisfactory insulin reaction after the first injection with diminution in craving and improvement in behavior was observed in 272 of 325 patients (84%). This method can be employed in the general hospital. Delirium tremens can be avoided or, if present, may be rapidly interrupted. There is no necessity for the "tapering off" technique with this treatment. The use of sedatives, hypnotics, or narcotics is contraindicated in the treatment of alcohol addiction.

Endokrinologie, Leipzig

28:129-256 (Nos. 3 & 4) 1951. **Partial Index**

Clearance Tests for Chorionic Gonadotrophin. L. Lajos and K. Páli. —p. 129.
*Menstruation Induced During Menopause by Desoxycorticosterone Acetate. V. Köhler and W. Münich.—p. 137.
*Addison's Disease and Pernicious Anemia. F. Boenheim.—p. 140.
Role of Hypophysis in Formation of Constitutional Types. J. A. Schneider.—p. 161.

Menstruation Induced by Desoxycorticosterone Acetate During Menopause.—Desoxycorticosterone or its acetate influences the sex organs. It has accelerated sexual maturation in mice and promoted the growth of the uterus in young rabbits. In castrated rats who have undergone adrenalectomy, it has been known to exert a folliculinizing and luteinizing effect. At the medical clinic of the University of Würzburg it was possible to observe the influence exerted by desoxycorticosterone acetate on the genital system, when it was administered for various disorders, particularly for gastric and duodenal ulcer in women between 20 and 65. With a daily dose of 20 mg., menstruation was often brought on from two to five days before the usual period. Furthermore, menstruation recurred in six women between 54 and 64 who had not menstruated for years. A table presents data on age, duration of menopause, dosage of desoxycorticosterone acetate, and duration, amount, and painfulness of menstruation produced by desoxycorticosterone acetate. The relation of desoxycorticosterone to the endometrium presupposes a complex action mechanism, and the authors suggest possible interrelated functions.

Addison's Disease and Pernicious Anemia.—In the classic description by Addison of the disease named after him, anemia is given as the cause. Later the combination of severe anemia, particularly of pernicious anemia and Addison's disease (suprarenal insufficiency), has been repeatedly denied or ignored. However, the combination has been mentioned by Biermer, by Bittorf in one of a series of cases of chronic Addison's disease, and more recently (1949) by de Gennes and several other French investigators. In the case described by these French investigators, temporary suprarenal insufficiency accompanied pernicious anemia. The diagnosis was established by the demonstration of diminished 17-ketosteroids in the urine. The suprarenal insufficiency subsided following effective treatment of the pernicious anemia, and the authors assume that the suprarenal insufficiency was of the functional type. A new case of concurrence of pernicious anemia and suprarenal insufficiency is reported in this paper. Despite the rarity of this combination it must be decided whether the connection is causal, as was originally supposed. Stephan contended that prolonged existence of suprarenal insufficiency almost invariably results in serious anemia and that the diseases are related. Boenheim does not agree with Stephan; he stresses the essential difference in the etiology of these two diseases but nevertheless admits possible connections between them.

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Hospital, Rio de Janeiro

39:757-904 (June) 1951. **Partial Index**

*Good Tolerance and Favorable Results of Intravenous Iron Therapy. N. Passarelli.—p. 775.
*Immunization Against Influenza. J. G. Lacorte.—p. 785.
*Intradermal Reaction with Polysaccharide Fraction Isolated from Culture of Leishmania Brasiliensis in Cases of Leishmaniasis Americana. J. Pellegrino.—p. 859.

Results of Intravenous Iron Therapy.—A new iron preparation, sodium-di(α,μ-dihydroxy-β,β-dimethyl-butyrate)-ferrate, containing 10 mg. of trivalent iron per cubic centimeter, was administered intravenously to 16 patients aged 14 to 57, with hypochromic-microcytic, normochromic, or pernicious (macrocytic) anemia. The anemia was due to verminosis, nutritional deficiency, hemorrhages from gastroduodenal ulcer or pregnancy. A dose of 2 cc. of the preparation was given either daily, every other day, or twice a day, for a total of six to 93 injections, according to the response of the blood. The injections were well tolerated. No immediate or late untoward reactions were observed after a total of 269 injections. Hemoglobin and erythrocyte levels in blood increased in the patients with hypochromic anemia. Pernicious anemia did not respond to intravenous iron therapy. Among the other cases there were favorable results in six and negative results in three. In one case, resistance to iron therapy developed. In two cases of severe anemia an initial partial improvement, with rise of erythrocyte count and hemoglobin level, was followed by lack of response to the drug. In another case, the blood picture improved after administration of vermifuges followed by oral iron therapy, which was then well tolerated. The author concluded that intravenous injection of iron is indicated in all the cases of iron deficiency that do not respond to, or do not tolerate iron by mouth.

Immunization Against Influenza.—The Virus Research Center of the Oswaldo Cruz Institute in Rio de Janeiro supplied 560,435 doses of influenza vaccine from 1945 until March 1951. These gave satisfactory immunizing results. The vaccine contains viruses A and B (strain PR8 and LEE) and FM-1 of type A'. The virus is inactivated with formaldehyde, in 1:10,000-1:5,000 dilution. Single doses of 1 cc. are administered subcutaneously. They cause immunity lasting six months. Reactions caused by the vaccine are rare, and there are no contraindications. Incidence of influenza was smaller among those who were vaccinated during the epidemic outbreaks of 1945, 1949, and 1951. Among the difficulties in the preparation of vaccines are the multiplicity of types and strains of viruses isolated during different epidemics, a fact that shows the necessity of studying influenza on an international basis to understand its epidemiology and to prepare vaccines having the adequate antigenic structure. To this end, strains of viruses from all over the world are sent by laboratories to the World Center for Influenza in London for study.

Intradermal Reaction for Leishmaniasis Americana.—Pellegrino used Fuller's technique for isolating the polysaccharide fraction of Leishmania brasiliensis. With this fraction he made intradermal inoculations in two cases of mucocutaneous leishmaniasis. Intradermal inoculation was also done with an antigen prepared by suspension of a culture of Leishmania brasiliensis in sodium chloride solution containing sodium ethylmercurithiosalicylate (merthiolate®) in the proportion of 1:5,000. The reaction was strongly positive in both patients and with both antigens. In six normal persons the reaction was negative.

Klinische Wochenschrift, Heidelberg

29:397-428 (June 15) 1951. **Partial Index**

*Dualistic Endocrine Output of Insular System in Persons with Normal Carbohydrate Metabolism and in Patients with Disturbances of Carbohydrate Metabolism. H. Ferner.—p. 397.
Electroencephalographic Observations in Internal Medicine. J. Moeller and O. R. Mantz.—p. 400.
Streptokinase: Mechanism of Action and Possibilities of Clinical Application. T. Halse.—p. 406.

Dualistic Endocrine Output of Insular System.—According to Ferner, there is a functional antagonism corresponding to the cytological dualism presented by the islands of Langerhans. Glucagon, a glycogenolytic principle that increases the blood sugar, originates in the alpha cells, while the beta cells produce insulin. The quantitative proportion between the alpha and beta cells in a normal adult is 20% alpha cells and 80% beta cells. This ratio occurs only when carbohydrate metabolism is normal, as shown by the physiological level of the blood sugar, and any change in this ratio is associated with a disturbance of the carbohydrate metabolism. Progressive hyperinsulinism develops in patients with insuloma that consists nearly exclusively of hyperactive giant beta cells. In diabetes mellitus produced experimentally in animals by alloxan injections, partial pancreatectomy, or administration of massive doses of extracts of anterior pituitary lobe, as well as in patients with diabetes mellitus, the ratio between alpha and beta cells is changed in favor of the alpha cells, from which the principle originates that increases the blood sugar. The significantly increased number of alpha cells is the proximate cause of the hyperglycemia. The suggestion seems to be justified that a "diabetogenic" change in the alpha-beta cell ratio may occur in diabetes mellitus under the influence of factors outside the pancreas.

Lancet, London

1:1287-1330 (June 16) 1951

Nucleic-Acid Content of Cell. J. N. Davidson, I. Lesslie and J. C. White.—p. 1287.
Spigelian Hernia: Hernia Through Linea Semilunaris: Report of Four Cases. C. Wakeley and P. Childs.—p. 1290.
Choice of Conservative or Surgical Treatment in Bleeding Peptic Ulcer. J. Pedersen.—p. 1292.
Metabolic Disorders in Head Injury: Hyperchloraemia and Hypochloruria. G. Higgins, W. Lewin, J. R. P. O'Brien and W. H. Taylor.—p. 1295.
Special Clamps for Simplifying Gastrectomy Technique. D. L. Stevenson.—p. 1300.
Emotional Faint. A. D. M. Greenfield.—p. 1302.
Complete Inversion of Appendix. T. H. Boon and J. C. Sibley.—p. 1304.
*Aetiology of Dupuytren's Contracture. E. G. Herzog.—p. 1305.
Fatal Poisoning by Inhalation of Carbon Tetrachloride (Thawpit). E. B. Love and A. A. Miller.—p. 1306.

Etiology of Dupuytren's Contracture.—Herzog saw 20 cases of Dupuytren's contracture at a 150-bed hospital in the course of two years. Since many patients asked compensation on the ground that hard work had caused the contracture, the author investigated this problem. Many literature reports suggest a hereditary predisposition, and a few observers recognize trauma from hard work as a possible contributory cause. Herzog investigated the incidence of Dupuytren's contracture among 1,000 steelworkers, 1,000 miners, and 1,000 clerks. The respective figures for these groups were 24, 22, and 19. It was noted that most of the cases of Dupuytren's contractures occurred in men over 40, and, considering only these, the percentages of incidence were 4.3%, 4.6%, and 3.75% for the three aforementioned groups. The incidence varied greatly in different groups: for instance, two cases were found in 25 bank clerks, who were over 40, and no case among 136 miners, of whom 64 were over 40. For this reason the author feels that the slight difference in the incidence between clerks and workmen is of no significance. He concludes that his investigation has produced no evidence that work in mines or steel mills leads to Dupuytren's contracture. He does not think that claims for compensation are justified.

Practitioner, London

166:425-526 (May) 1951

Heredity and Environment in Causation of Foetal Malformation. L. S. Penrose.—p. 429.
Congenital Heart Disease. J. W. Brown.—p. 436.
Congenital Abnormalities of Gastro-Intestinal Tract. L. Barrington-Ward.—p. 443.
Congenital Abnormalities of Renal Tract. J. C. Anderson.—p. 450.
Congenital Abnormalities of Nervous System. J. Craig.—p. 461.
Congenital Abnormalities of Lower Limbs. B. McFarland.—p. 468.
Congenital Abnormalities of Skin. R. T. Brain.—p. 480.
Biopsy in Malignant Disease. H. Ogilvie.—p. 488.
Pathological Sleep. W. A. O'Connor.—p. 494.

166:527-628 (June) 1951. **Partial Index**

Problem of Hypertension. H. Goldblatt.—p. 531.
Drug Treatment of Hypertension. I. G. W. Hill.—p. 541.
Diet and Hypertension. G. W. Hayward.—p. 548.
Hypertension as Manifestation of Endocrine Dysfunction. J. S. Richardson.—p. 556.
Surgery of Hypertension. A. M. Boyd.—p. 564.
The Eye in Hypertension. W. J. B. Riddell.—p. 571.
Hypertension and Life Assurance. H. N. Collier.—p. 577.

BOOK REVIEWS

Diabetes Mellitus: Principles and Treatment. By Garfield G. Duncan, M.D., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia. With collaboration of Ferdinand Fetter, M.D., Assistant Professor of Medicine, University of Pennsylvania, Philadelphia, Perry S. MacNeal, M.D., Associate in Medicine, Jefferson Medical College, Philadelphia, Barkley Beidleman, M.D., Assistant in Medicine, Jefferson Medical College, Philadelphia, and Martha A. Hunscher, B.S., Director of Food Clinic, Pennsylvania Hospital, Philadelphia. Cloth. $5.75. Pp. 289, with 31 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C.2, 1951.

Dr. Duncan's new contribution to the textbook literature on diabetes mellitus is a valuable guide for any physician. The style of the volume is simple, and its contents are arranged in orderly fashion. It is direct, concise, practical, accurate, and sound in its approach. The wide experience of the author is detailed in so well-organized and clear a manner that his book will be a refreshing aid to all who are not too familiar with this fascinating disease but who wish to take advantage of modern methods of diagnosis and treatment.

There are no superfluous details or elaborations, yet no important phases are neglected or omitted. No personal preferences are stressed, and no prejudice is entertained. Tables and diagrams are included in generous numbers. For the most part they are informative and useful. Illustrations, particularly of pathological phenomena, are faithfully descriptive.

In conformance with the vast majority of experts in the field, the author insists on the wisdom of maintenance of good control as a probable preventive of complications. He stresses the undesirability of obesity, the value of weight reduction and even some degree of undernutrition in treatment, and the preservation of sugar tolerance by control of weight and sugar levels. The diet system outlined is quantitative, with a choice of weighing or measuring systems. The new food exchange system approved by the American Diabetes Association is advised. Indications for various types of insulin and the clinical results of their application are outlined clearly. Complications, surgical management, and vascular disease are given adequate emphasis. There is an excellent review of the important endocrine relationships in the physiology and clinical association of factors affecting regulation of the sugar balance. Significant references to the literature conclude each chapter.

A large amount of valuable pertinent information has been condensed into a relatively small volume with discrimination. It may be recommended to students of the disease as a conservative and complete modern treatise on the subject.

Post-Graduate Lectures on Orthopedic Diagnosis and Indications. By Arthur Steindler, M.D., F.A.C.S., Professor of Orthopedic Surgery, State University of Iowa, Iowa City, Iowa. Volume II. Section A: Paralytic Disabilities; Section B: Static Disabilities. Cloth. $6. Pp. 198, with 140 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 49 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, 1951.

Dr. Steindler is well-known in the field of orthopedic surgery. His many writings have made him familiar to all orthopedists. His writings are based on his vast experience and are evaluated by a keen scientific mind. This book is a series of lectures for postgraduate students in orthopedic surgery. This is part of a series of monographs and contains a section on paralytic disabilities and a section on static disabilities.

Besides speaking from his own experience, the author also presents all concepts that are considered of value at the present time. There is a nicely balanced record of the conservative and operative treatment of the conditions he discusses. Under the subject of paralytic disabilities he covers poliomyelitis and its etiology, pathology, diagnosis, and treatment. He discusses paralytic scoliosis. The fourth lecture concerns spastic paralysis. Under static disabilities he discusses low back pain, including idiopathic low back pain as well as back pain due to intervertebral discs. He also discusses idiopathic scoliosis.

There is a comprehensive lecture on internal derangements of the knee. The mechanics of the foot are discussed. In treatment the author refers to the usual recognized conservative and operative measures. The subject matter is well arranged, and the type and paper are of excellent quality. The illustrations are clear, well-selected, and well-reproduced. There is a selected bibliography following each chapter. Dr. Steindler writes in a simple and clear manner. This book expresses his concepts much more clearly than did some of his original scientific articles.

The reviews here published have been prepared by competent authorities and do not represent the opinions of any official bodies unless specifically stated.

Handbuch der inneren Medizin. Herausgegeben von G. v. Bergmann und W. Frey. Unter Mitwirkung von H. Schwiegk. Begründet von L. Mohr und R. Staehelin. Band II: Blut und Blutkrankheiten. Neu bearbeitet von Ludwig Heilmeyer, Dr.med., O. O. Professor, Direktor der medizinischen Universitätsklinik, Freiburg i. Br., und Herbert Begemann, Dr.med., Leiter des hämatologischen Laboratoriums der medizinischen Universitätsklinik, Freiburg i. Br. Band VIII: Nieren und ableitende Harnwege: Die hämatogenen Nierenerkrankungen. Die ein- und beidseitig auftretenden Nierenkrankheiten. Erkrankungen der Blase, der Prostata, der Hoden und Nebenhoden, der Samenblasen, funktionelle Sexualstörungen, bearbeitet von Walter Frey und Friedrich Suter. Fourth edition. Cloth. Pp. 1179, with 474 illustrations; 1167, with 193 illustrations. Springer-Verlag, Reichpietschufer 20, Berlin W. 35 (West Berlin); Neuenheimer Landstrasse 24, Heidelberg; Göttingen, 1951.

This is Volume 2 of the well-known "Manual on Internal Medicine" originally edited by Mohr and Staehelin. It could be called a system rather than a manual, for it covers the field of internal medicine in detail, with extensive documentation. It is a useful reference work. The present editors are recognized internists fully competent to carry on the traditions of the original work. In the introductory remarks the editors comment on the desirability of the Morgagnian concept of pathological anatomy as a basis for the study of disease but point out that the blood is not an organ and that its diseases are reflections of abnormalities in the blood-forming organs. The work opens with a general section discussing the composition of the whole blood, including its total volume, the plasma, the general cytology and bone-marrow physiology, and the technique and general results of spleen and lymph-node puncture. Then follow chapters on the morphology and physiology of the erythrocyte system, the formation and destruction of red blood cells and hemoglobin, and a discussion of blood-grouping and transfusion. This is followed by discussions of the special diseases of the red blood cells, and the different types of anemia and polycythemia, their symptomatology, diagnosis, prognosis, and treatment. The leucocytes and the reticuloendothelial system are then discussed in their morphological and physiological aspects and in respect to hereditary and acquired diseases, with a special discussion of the x-ray treatment of Hodgkin's disease. There are sections on the hemorrhagic diatheses, the diseases producing abnormalities in clot formation, the aplastic and hypoplastic myelopathies, and blood parasites. An appendix on diseases of the spleen and the lymph nodes concludes the volume.

The book is attractively bound, and the paper and typography are excellent. The illustrations, many of them colored, are of high quality, and the text is not difficult to read. There is abundant evidence that the writers have consulted medical literature widely and have given due credit to contributors. While the arrangement differs somewhat from American works of similar scope, it is logical and satisfactory. The book can be recommended as a competent and well-documented survey of the field.

Volume 8 of the fourth edition is contributed by competent workers in the field of kidney diseases and diseases of other sections of the genitourinary tract. The volume opens with a historical chapter that covers the period of Malpighi and also discusses the work of his successors, notably Ruysch, Haller, Bowman, Johannes Müller, Bichat, Henle, Ludwig, Bright, Virchow, Abel, and Volhard and Fahr. The chapter contains illumi-

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nating discussions of the different forms of Bright's disease. Following this chapter there are sections dealing with anatomic and physiological bases of the different types of hematogenous kidney diseases, with discussions of the various chemical and functional tests. Then follows a short section on the theories of urine formation, with special stress on such modern concepts as contact and electrical potential and discussions of the important experimental and clinical studies of urinary secretion. Succeeding sections cover the clinical aspects of the nephropathies, with competent discussions of such characteristic symptoms as hematuria, pyuria, renal hypertension, edema, and uremia. There are adequate discussions of the course, prognosis, and treatment of kidney disease and special sections on the arteriosclerotic contracted kidney. Dr. Suter, in the final third of the volume, discusses competently the so-called surgical kidney affections: diseases of the bladder, the prostate, the testis and epididymis, the seminal vesicles, and functional sexual disturbances.

As in preceding volumes the book is attractively bound, the paper is of excellent quality, the typography is clear, and the accompanying charts and tables, including an elaborate list of foodstuffs with their caloric values and chemical composition, are well-chosen and helpful. There are gross and microscopic illustrations of the normal kidney and the nephropathies and some excellent colored illustrations of cystoscopic findings. The literature is extensive, and there are good name and subject indexes. The articles are clearly written, and the work should serve not only as a textbook but also as a reference book.

A Review of Medicine by Members of the Faculty, Northwestern University Medical School. Edited by Benjamin Boshes, M.D., M.S., Ph.D., Associate Professor of Nervous and Mental Diseases, Northwestern University Medical School, Chicago. Sixth edition. Cloth. $15. Pp. 814. [University Bookstore, Northwestern University], 434 E. Huron St., Chicago 11, 1951.

This large volume is essentially an outline of clinical medicine, including surgery, obstetrics and gynecology, and the various medical and surgical specialties, intended to assist medical students in preparing for examinations and to provide interns, residents, and general practitioners with a ready source of reference for a wide variety of medical problems. The value of the work appears to be established, since it has gone through so many editions over a period of 18 years.

The first edition (1934) consisted of material given in a series of lectures at Northwestern to prepare students for the annual examinations for the Cook County Hospital internship. Through subsequent editions, new subjects and new sections were added, extraneous material was deleted, and the format was modified. A compiete revision and reorganization was accomplished with the fourth edition, in 1940. This edition is, again, essentially a new book. New sections have been incorporated, other sections have been rewritten, and many new names appear in the list of contributors. This is neither a textbook nor a monograph. Its original purpose and style remain. It is an elastic compilation of data taught in the classrooms of Northwestern, each section written by a specialist. The style of presentation usually follows a modified outline form, but some sections are in essay style. The content has been brought completely up-to-date.

The book is large and bulky, but the type is good, and the spacing adequate for quick reading. There is a satisfactory index, but no bibliography and no illustrations. For the student or intern who wishes to review for state board examinations, this volume will require supplementation, since it does not contain sections on the preclinical sciences.

Selected Writings of Sir William Osler, 12 July 1849 to 29 December 1919. With introduction by G. L. Keynes, M.D., F.R.C.S. Cloth. $4. Pp. 278. Oxford University Press, 114 5th Ave., New York 11; Amen House, Warwick Sq., London, E.C.4, 1951.

One of the best things that could happen to a medical student would be to become interested in the life and work of Sir William Osler. His influence on the medical profession is still strong, although he has been dead more than 30 years. His life provides a pattern that physicians could well follow. While a bibliography of his writings would contain hundreds of items, in this book are collected only a few of his more or less philosophical essays. These essays were chosen by a committee "to give the medical student a taste of Osler." They will find here, not the pathologist or the clinical professor, but Osler the essayist and historian. The introductory chapter comprises an interesting but short biography.

The Mark of Oppression: A Psychosocial Study of the American Negro. By Abram Kardiner, M.D., and Lionel Ovesey, M.D. (Research on which this book is based was done with technical assistance of William Goldfarb, Robert Gutman, Ethel D. Kardiner, and Zeborah Suesholtz.) Cloth. $5. Pp. 396. W. W. Norton & Company, Inc., 101 Fifth Ave., New York 3, 1951.

In the Mark of Oppression, Kardiner and Ovesey have given a psychodynamic analysis of Negro adaptation that furnishes a clear understanding of why Negroes react to many situations in the way they do. This careful scientific study, using a new methodology, is a contribution to the study of behavior problems that is as important in what it reveals about other segments of the population as it is significant in evaluating the basis of Negro reactions. According to the authors, "This book is conceived and written as an inquiry, not as a polemic. It is conceived and written on the premise that group characteristics are adaptive in nature and therefore not in-born but acquired."

The source material for this book is an intensive case study of 25 Negroes, all obtained by the psychoanalytic interview method. An adequate basis for intelligent understanding and digestion of this material is presented in Part 1: The White Man and the Negro, A Comparative Sociology, The Social Environment of the White Man and the Social Environment of the Negro. This in itself is a noteworthy and scientifically sound contribution. Part 2: the personality studies of 25 Negroes drawn from the lower, middle, and upper classes, the adolescent, and neurotic sampling give ample material for extensive elaboration.

Rorschach test interpretations made by William Goldfarb substantiated the findings and hypotheses of Kardiner and Ovesey. In the synthesis of experimental data, the authors make the following observation: "Nor must we overlook what is perhaps the most important lesson in this study. The defects of adaptation that we have described, together with their social sources, make a dismal picture of human misery, one for which it is hard to find a parallel. However, in spite of its defects when compared to white standards, we must not forget that in the face of such hardships it is a heroic achievement to be able to adjust and to survive. The authors have often been amazed at the remarkable ingenuity and stamina that most of these subjects showed, and each of the authors has privately thought that under similar conditions of living, neither could have done as well."

Kardiner and Ovesey have made a valuable contribution in a field in which they are recognized authorities. They have also performed a signal service to mankind perhaps at present not fully appreciated.

All who are interested in man and his relation to his fellow men can read this book with profit.

Administrative Medicine. Haven Emerson, A. M., M.D., editor. New edition. Cloth. $10. Pp. 1007. Thomas Nelson & Sons, 19 E. 47th St., New York 17; Parkside Works, Dalkeith Road, Edinburgh 9, 1951.

This book is intended to be used as a reference by medical administrators and by advanced students who are preparing for work as medical administrators. It has the usual advantage and disadvantages of a compilation. The breadth of its scope is such that no one person could have written it. Dr. Emerson had done well in the choice of the various experts who have contributed, and he has succeeded in producing a harmonious whole. The authors are men of actual experience in the field covered. They are men of sane and conservative views and completely worthy to be considered experts in their respective fields. Dr. Emerson is well-known as a man of sound judgment in matters pertaining to health and medical administration. Any views that he may have sponsored in a book of this sort are well worthy of earnest consideration by those in positions of responsibility.

Here is a book which should become a *vade mecum* on the desk of medical administrators. So far as we know, there is no other book available covering exactly this field in so complete a manner. We recommend it highly as a well-written, carefully planned and edited book loaded with useful information and sound administrative principles. It should have wide use.

QUERIES AND MINOR NOTES

REFRIGERATED BLOOD AND TRANSFUSIONS

To the Editor:—*Is refrigerated blood as free of adverse reaction in the patient when given at room temperature or body temperature as it is when given directly from the refrigerator without preliminary warming? Does refrigerated blood cause any more reactions than warm blood from the donor?*

H. S. Puckett, M.D., Stillwater, Okla.

Answer.—Refrigerated blood may be given to a patient, under ordinary circumstances, by standard methods and at a normal rate (about 10 cc. per minute) without fear of adverse reaction, even though the blood is not warmed to room temperature or to body temperature before administration. Numerous measurements have shown that, by the time the blood has traversed the relatively long recipient's tube and the needle, its temperature has risen from the original 4 to 6 C., at which it may leave the refrigerator, to 15 to 20 C. It is then warmed relatively rapidly as it flows into the body, so that there is no appreciable effect on the patient. There is no evidence that increase in reaction rate results from this. In fact, blood that has been kept cold up to the time of administration is probably safer, for if the blood is warmed too rapidly, as in a water bath at over 40 C., there is greater likelihood that many of the cells, particularly those in contact with the glass, will be destroyed and a higher percentage of hemolysis will result. One other danger is that, if the blood is kept standing at room temperature or in a 37 C. water bath for a considerable time, any contamination that has occurred will permit the growth of organisms and lead to a serious reaction. Even in patients with shock, there is no need to warm the blood.

There are two possible dangers from the use of cold blood. If the transfusion is given very rapidly, as occasionally occurs on the operating table, with the injection of a pint (473 cc.) of blood at a temperature of 6 to 10 C. within a period of 15 or 20 minutes, the patient's extremity into which the blood is running may be rapidly cooled and this may cause a mild sensation of chilliness. Even under these circumstances, one rarely sees any signs of reaction. The other possibility that has some times been considered serious is that, if a patient has a high titer of cold agglutinins, as after viral pneumonia, the injection of refrigerated blood may allow such cold agglutinins (which occasionally are active even at 20 C.) to produce clumping of the infused cells and result in a transfusion reaction. It may, therefore, be advisable to administer a transfusion relatively slowly (certainly not over 10 cc. per minute) to a patient known to have cold agglutinins, or, if these are active even at room temperature, to warm the blood before transfusion.

The common practice of heating the blood rapidly after it has been removed from the refrigerator, especially by immersing it in a pan of hot water, is to be avoided under all circumstances, because of the danger of destroying red cells by rapid changes in temperature or even heating in excess of 37 C. Also the practice of allowing blood to stand for several hours at room temperature, until it is decided whether the patient is to receive a transfusion, should be avoided. Finally, returning blood, once warmed, to the refrigerator should not be permitted. Such drastic changes in temperature are likely to cause destruction or serious injury to many of the red cells, with loss of value to the recipient when such blood is subsequently used.

ALBINISM

To the Editor:—*Can anything be done to an albino child to improve his tolerance to light?*

F. Vela Gonzalez, M.D., Monterrey, N. L., Mex.

Answer.—Complete albinism results from congenital absence of pigment throughout the entire body. The skin is milky white or has a pinkish tinge; the hair is white or whitish yellow, and there is a similar deficiency of pigment in the eyes. The iris has a dull, pearly gray appearance, and the pupil may appear red in natural light. Unfortunately, because of the absence of pigment, nothing can be done to improve tolerance of an albino child to light. Standard textbooks make such statements as the following: "As may readily be inferred, albinismus cannot be lessened or influenced by treatment—it is, in fact, without remedy." The only measures that are helpful are protection of the skin from excessive exposure to sunlight and especially protection of the eyes from excessive amounts of light by use of sun glasses.

ATROPHIC PHARYNGITIS

To the Editor:—*A woman, 66, has complained of dryness of her throat for four months. Her family physician has prescribed every antibiotic and other type of lozenge available on the market with no effect. When I saw the patient two months ago, the posterior pharyngeal wall had a dry, glistening appearance, with obvious atrophy of the mucosa and some small, reddish, granular nodules. I have seen this condition frequently in elderly women. Is this an atrophic pharyngitis on the basis of an endocrine disturbance or a degenerative process?*

M.D., Massachusetts.

Answer.—In atrophic pharyngitis (pharyngitis sicca), an entity often associated with atrophic rhinitis, the posterior wall of the pharynx has a lusterless, glazed appearance in mild cases and there is advanced atrophy of the mucous membrane, with dry crust formation and fetor, in advanced cases. The patient afflicted with atrophic rhinitis has a sense of considerable dryness in the throat. To dislodge the adherent secretion on the posterior pharyngeal wall, some patients will make frequent attempts to clear the throat by hawking, retching and sometimes by vomiting. Consequently, a chronic sore throat is not an unusual accompaniment. Although the cause is unknown, occasionally an endocrine relationship is suggested by the basal metabolic rate. In elderly patients a more plausible explanation is that the disease is due to a degenerative process.

As in the case of atrophic rhinitis, treatment is directed toward the alleviation of symptoms, since it is currently impossible to regenerate atrophied pharyngeal mucous membrane. Medication is similar to that used for chronic pharyngitis. In conjunction with treatment of atrophic rhinitis, if this condition is present, treatment of the pharyngeal wall may include the local application of Mandl's solution or tincture of iodine in glycerin (1 to 7 parts). These preparations stimulate secretion. At the same time, potassium iodide may be given internally. An average dose is 10 drops of a saturated solution, to be taken three times daily with meals. The inspiration of warm, moist air from a kettle, vaporizer or basin helps moisten inspissated secretion. Attention to general health should, of course, receive consideration.

FAILURE IN SENSATION FROM BLADDER DISTENTION

To the Editor:—*A patient has no sensation of the need of emptying the bladder. He knows when the bladder is full only by feeling the end of the penis and when in bed by a pain in the left hip. I shall be grateful for suggestions for treatment in such a case.*

Louis L. Sherman, M.D., Oakland, Calif.

Answer.—Failure in sensation from bladder distention occasionally is observed as the first clinical sign of lesions involving the spinal cord. Among the possible diseases that might be mentioned are tabes, multiple sclerosis, neoplasm, and other lesions involving the central nervous system. In the absence of any other clinical data, it is impossible to make an exact diagnosis in this case or to advise treatment. The services of a competent neurologist are recommended, who, with the help of roentgenologic, urologic, and other data, could give accurate counsel.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any official bodies unless specifically stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

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PAROXYSMAL AURICULAR TACHYCARDIA

To the Editor:—*Since childhood I have been troubled with recurrent paroxysmal tachycardia. I am now 75 years old. Often, in turning my head to the left, a slight fainting feeling results. Just before and during the attack, the right carotid sinus region pulsates much more than does the left. Pressure on the carotid sinus does not stop the attack. Before an attack, there is a weak feeling in the umbilical region and little, if any, signs or symptoms in the region of the heart. There are no anginal or coronary obstruction symptoms, and none of any organic heart lesion. Blood pressure is a trifle above normal. Would procaine hydrochloride injection be indicated in the right or left carotid sinus if the attack lasts too long? Can you suggest any treatment to stop that abdominal starter from starting the auricle at double speed? I use cinchona alkaloids whenever needed. I eat five small meals a day, because I have noticed that a large meal (or a large evacuation) helps start an attack, especially in the morning. Please suggest treatment and prevention.*

M.D., Oklahoma.

Answer.—Any patient who has a history of recurrent attacks of rapid, regular heart action, setting in suddenly, having been present since childhood and displaying no evidence of organic heart disease, may be considered as having paroxysmal auricular tachycardia. Procedures such as pressure on the carotid sinus, pressure on the eye ball, the induction of gagging or vomiting, and attempted expiration with a closed glottis (Valsalva's experiment) may be often successful when used singly or in combination. When these measures fail and the tachycardia persists for hours, digitalis, quinidine or the highly potent mecholyl (dangerous in infants and elderly subjects) can be tried. There are also favorable reports on the use of neostigmine and phenylephrine (Neo-Synephrine®) hydrochloride. Procaine injection to the upper thoracic ganglions has been used in several instances, but it does not always stop the attack.

The purpose of all these measures is to stimulate the vagus or inhibit the cardiac accelerators. Injection to the carotid sinus would not serve such a purpose. One of the triggers in bringing on the attack is overdistention of the stomach or hypoglycemia. Nothing better than frequent small meals can be suggested. Self-medication is fraught with danger.

LEUKOPLAKIA BUCCALIS

To the Editor:—*A man, 57, has had leukoplakia buccalis for about half a year. It is especially pronounced on the left side of the tongue and cheek. It subsides somewhat after he abstains from smoking for a couple of weeks and becomes more pronounced a few days after he resumes smoking. Is smoking absolutely to be prohibited? What are the possibilities of the formation of a cancer? Is any therapy indicated?*

Samuel Barmak, M.D., Brooklyn, N. Y.

Answer.—Leukoplakia is a clinical term meaning "white plaque." It is the response of a mucous membrane to some form of chronic irritation. Smoking occasionally causes such a lesion. The case of which you write seems to fit this category. Certain forms of leukoplakia are considered to be "precancerous lesions." When, following microscopic examination, the pathologist reports "leukoplakia," he usually means more than a simple "white spot"; namely, there is evidence of dyskeratosis. A biopsy is indicated in any lesion that seems at all suspicious, particularly in those in which any thickening is found.

PROSTATIC HYPERTROPHY

To the Editor:—*Have estrogens or other hormones been tried to prevent hypertrophy of the prostate? Since estrogens are helpful in cancer of the prostate, it might be logical to use them in hypertrophy.*

J. Minkin, M.D., Bronx, N. Y.

Answer.—There is no way to prevent hypertrophy of the prostate. Hormones have never prevented or cured benign hypertrophy of the prostate; they have, however, been of great value in the treatment of cancer of the prostate.

A "SIXTH" LUMBAR VERTEBRA

To the Editor:—*An x-ray report was sent to me with a diagnosis of "6 lumbar vertebrae," and yet the x-ray films were taken of only the lumbosacral area, without a dorsal and chest view. One specialist, without making a count of the dorsal vertebrae, said that since there were six vertebrae with the appearance of lumbar vertebrae, the diagnosis was tenable. Indeed there were six visible vertebrae without evidence of any rudimentary rib structures. We would all like to know the criteria for making such a diagnosis and whether, if only 11 vertebrae with articulating ribs are shown by further x-ray studies, the vertebra in question should be called an extra lumbar or a 12th dorsal sans rib attachments.*

Don Dieter, M.D., Salina, Kan.

Answer.—The question as to the criteria for diagnosing a sixth lumbar vertebra is really a question in semantics rather than in radiology or anatomy, and if one is worried about it he can avoid the difficulty by substituting the term "non-rib-bearing presacral vertebra." The idea that an examination of the entire spinal column will resolve the difficulty is not sound, and it is an expensive procedure that ought to be avoided if possible. If a patient is found to have six non-rib-bearing presacral vertebrae and a short sacrum, it is common to describe the lowest nonsacralized segment as a lumbarized first sacral. If the sacrum appears to be of normal length, the extra segment is usually described as a sixth lumbar.

RUSTY NAIL WOUND

To the Editor:—*What is the best local treatment for a puncture wound of the sole of the foot by a rusty nail? The nail entered to a depth of a quarter of an inch, and no complications have set in.*

M.D., California.

Answer.—Bowen (*J. A. M. A.* **119**:413 [May 30] 1942) recommended the following treatment: 1. The foot is to be soaked for 15 to 30 min. in hot water to which tincture of soft soap is added. 2. It is dried carefully, and an area about 2 to 3 in. (5.08 to 7.62 cm.) in diameter around the wound is painted with an appropriate antiseptic. 3. The top layer of the skin is cut away around the wound, resulting in exposure of foreign matter (usually sand, rarely particles of sock, leather, rubber or concrete), which can be removed easily. 4. A dry dressing is applied. 5. If the wound is caused by a nail larger than a ten-penny nail, the patient should not walk for at least one or two days; but if a nail of lesser diameter is involved, he may walk at once.

In addition to the above local management, the appropriate use of tetanus antitoxin and tetanus toxoid (Skin Test Technic, Queries and Minor Notes, *J. A. M. A.* **139**:68 [Jan. 1] 1949) is indicated. Too much reliance must not be placed on the local and parenteral use of penicillin to prevent tetanus.

POLYCYSTIC KIDNEYS

To the Editor:—*A patient, 52, has polycystic kidneys. Her nonprotein nitrogen has been consistently normal despite the fact that x-rays show considerable diminution of kidney tissue. Blood pressure is normal; there is no edema; the daily amount of urine is normal, and body weight remains constant. The patient seems in good health. Textbooks are vague on the subject and give a gloomy prognosis. Can you suggest anything in the way of treatment?*

M.D., Florida.

Answer.—This patient has a good prognosis in view of her normal blood pressure and blood nonprotein nitrogen at age 52. If she is asymptomatic, there is no reason for any specific treatment for polycystic kidneys. Renal function should be checked from time to time, so that necessary dietary adjustments may be made. The urine should be watched for evidence of infection or hemorrhage. If the former occurs, antibiotic therapy is indicated varying with the nature of the micro-organism. Persons with polycystic kidneys may achieve a normal life expectancy if renal function is well preserved into the sixth decade.

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DISINFECTION OF BLOOD—CONTAMINATED LANCETS

To the Editor:—*We are concerned about the possibility of the transmission of homologous serum jaundice through skin punctures. For this reason, we started autoclaving our skin puncture devices. The result was dulling of the blade. We switched to dry sterilization and found that our corks became charred. Can you suggest any germicide known to be effective that would not dull the blades or have other disadvantages? A recent pamphlet from the Bard Parker Company, extolling the virtues of their formaldehyde disinfectant, has suggested the possibility that it or some other material might be adequate.*

Douglas Warner, Ph.D., Santa Barbara, Calif.

Answer.—Although Rhodes and van Rooyen (Textbook of Virology, New York, Thomas Nelson & Sons, 1949) state that virus-contaminated material may be sterilized by immersion in chemical solutions, many investigators believe that such measures are not adequate for certain destruction of the viruses, particularly in the presence of organic substances.

Neefe (*M. Clin. North America*, Philadelphia Number, November, 1946) reported that the virus of homologous serum jaundice, in human albumin, is inactivated by heating for 10 hours at 60 C. (140 F.). Heat is therefore recommended for the disinfection of blood-contaminated lancets, needles, and syringes, despite its deleterious effect on the temper of the metals. The piercing properties of lancets and needles are easily restored by use of an emery stone. The straight Hagedorn No. 6 needle is probably more adaptable to reconditioning than is the type of blade indicated above. The point of the lancet should not be inserted into a cork during disinfection or sterilization procedures.

Immersion of previously cleaned instruments in boiling water for 15 minutes will destroy the virus of homologous serum jaundice. Dry heat sterilization requires a longer interval at a comparable temperature. Specific procedures employing heat disinfection of lancets, needles, and syringes are described in The Journal of June 11, 1949, page 579, and Dec. 2, 1950, page 1226.

CALCIFICATION OF SOFT TISSUES

To the Editor:—*A man, 50, has calcification of the tissues of one hip as indicated by x-rays. The hip was a little swollen, but there was no pain. In the course of his work, he repeatedly strikes this part of his body against a machine. Please advise whether any treatment is available.* *M.D., Connecticut.*

Answer.—Calcification of the soft tissues around the hip is rather infrequently seen. If the calcification is lateral to the greater trochanter, it may represent calcium deposits in the trochanteric bursa, which is similar to calcium deposits in other bursa of the body, particularly in the region of the shoulder. Sometimes these respond to x-ray therapy, but occasionally surgical excision is necessary for the eradication of the condition. But, assuming the patient is having no pain and the diagnosis is definitely established as bursitis, probably no treatment would be necessary. If the calcium is deposited elsewhere, particularly around the neck of the femur, it probably is a case of calcification of the muscles and might be the forerunner of myositis ossificans. However, without having an opportunity to review the x-rays, it is impossible for one to make an accurate diagnosis.

DUOCHROME REFRACTION TEST

To the Editor:—*I desire information on a method used in refraction of the eye, to see if the prescription is correct. In this test, red and green letters are shown the patient wearing the glasses; if he sees one of the colors best, he is supposedly on the myopic side; if the other letters are seen best, he is on the hyperopic side. I have not been able to find this information in any book at my disposal.*

L. Murphy Henry, M.D., Fort Smith, Ark.

Answer.—The emmetropic light-adapted eye is most sharply focused for the spectral color of highest luminosity, which, for the average eye, is yellow of 555 mμ wavelength. When thus focused, red and green rays at equal wavelength distance from this point of the spectrum form aberration disks of equal diameter. This observation, made by Helmholtz, is the basis of the original duochrome refraction test introduced by Clifford Brown of London in 1927 and described by H. H. Emsley (Visual Optics, London, Hatton Press, 1936). The application has been simplified in the projectochart apparatus, which contains an accessory transparent slide, half red and half green of the proper hues. When in use the visual chart is divided laterally by superimposed red and green light. The eye, if emmetropic or made so, sees the letters equally well on both backgrounds, but, if excessive plus power has been added, the letters on the red background will be in focus nearer to the retina and will be seen more clearly than the letters on the green background, and vice versa. The indication, therefore, is to add minus power if the letters on the red background appear clearer and plus power when the letters on the green background are the more distinct. In the brochures furnished by manufacturers of projectocharts, this technique is fully explained. Following a suggestion of Maddox, Lebensohn has adapted the duochrome principle to the near vision test chart as a help in the precise determination of the presbyopic addition (*Am. J. Ophth.* **32**:22 [Jan.] 1949).

AMENORRHEA FOLLOWING MISSED ABORTION

To the Editor:—*Why does a woman suffering a missed abortion not menstruate, even though the condition may go on for months or years? I am anxious to know the various opinions that this question should bring forth.* *M.D., Illinois.*

This inquiry was referred to two authorities, whose respective replies follow.—Ed.

Answer.—In missed abortion with death of the fetus, there still may be placental tissue attached to the uterus, which may give rise to enough estrogen production to suppress menstruation.

Answer.—The endocrinal mechanism that regulates cyclical activity in the ovary and reproduction is only partially understood. Following is the most reasonable and current explanation: In the normal cycle, FSH from the anterior lobe of the pituitary gland stimulates follicle growth. Prior to ovulation a widespread atresia of the secondary follicles occurs, which eliminates all except the dominant follicle and provides a spurt in estrogen production which stimulates the release of LH by the pituitary. This gonadotropin induces ovulation of the dominant follicle and corpus luteum formation. The life of the corpus luteum is about 14 days, and its regression results in a drop in the level of estrogens and progestin which brings on menstruation.

If pregnancy occurs, chorionic gonadotropin elaborated by the young conceptus prolongs the life of the corpus luteum until such time as the placenta is sufficiently developed to take over the production of the steroid hormones. Experimentally, chorionic gonadotropin administered to a woman during the progestational phase of the cycle will postpone menstruation 10 days or longer, because the corpus luteum remains functional.

After the death of the embryo in missed abortion, viable chorionic tissue may continue to produce progestin for many weeks. This can be followed by the quantitative determination of urinary pregnanediol. When the pregnanediol output has reached a low level or disappears completely, the uterus usually expels its contents. The disappearance of progestin allows the LH factor in the pituitary to again assert itself, and follicular activity, ovulation, and menstruation are resumed.

MUSCULAR DYSTROPHY

To the Editor:—*What should be done in the way of supportive therapy in muscular dystrophy? Is intensive physical therapy requiring hospitalization beneficial?*

Warren G. Strout, M.D., Pittsfield, Maine.

Answer.—Unfortunately, no form of treatment is of value in cases of progressive muscular dystrophy. There is no evidence that physical therapy has any beneficial effect. Certainly there would be no justification for hospitalization and intensive therapy of this type.

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